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GUIDELINES

The Japanese Clinical Practice Guidelines for Management of Sepsis and Septic Shock 2024

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Abstract
The 2024 revised edition of the Japanese Clinical Practice Guidelines for Management of Sepsis and Septic Shock (J-SSCG 2024) is published by the Japanese Society of Intensive Care Medicine and the Japanese Association for Acute Medicine. This is the fourth revision since the first edition was published in 2012. The purpose of the guidelines is to assist healthcare providers in making appropriate decisions in the treatment of sepsis and septic shock, leading to improved patient outcomes. We aimed to create guidelines that are easy to understand and use for physicians who recognize sepsis and provide initial management, specialized physicians who take over the treatment, and multidisciplinary healthcare providers, including nurses, physical therapists, clinical engineers, and pharmacists. The J-SSCG 2024 covers the following nine areas: diagnosis of sepsis and source control, antimicrobial therapy, initial resuscitation, blood purification, disseminated intravascular coagulation, adjunctive therapy, post-intensive care syndrome, patient and family care, and pediatrics. In these areas, we extracted 78 important clinical issues. The GRADE (Grading of Recommendations Assessment, Development and Evaluation) method was adopted for making recommendations, and the modified Delphi method was used to determine recommendations by voting from all committee members. As a result, 42 GRADE-based recommendations, 7 good practice statements, and 22 information-to-background questions were created as responses to clinical questions. We also described 12 future research questions.

KEYWORDS
evidence-based medicine, infection, intensive care, organ failure, systematic review

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BACKGROUND

Sepsis is a serious condition leading to deaths, and the World Health Organization designated it as an issue to be addressed worldwide in 2017. The Japanese Clinical Practice Guidelines for Management of Sepsis and Septic Shock 2024 (J-SSCG 2024) provides information on diagnosis, treatment, and patient and family care to patients with sepsis and all related healthcare providers, aiming to improve the quality of medical treatment and mortality rate. The first edition of the J-SSCG was published in 2012, with the current revision being the fourth edition. Upon creating the J-SSCG 2024, we carefully selected critical clinical issues (clinical questions, CQs) that are mainly related to sepsis and reduced the number of CQs from 118 in the J-SSCG 2020 to 78. Utilizing our accumulated expertise in creating guidelines, we comprehensively collected the latest evidence, which was then analyzed using standard methods and evaluated using objective methods in accordance with the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system. Additionally, we aimed to create "user-friendly guidelines" that provide useful information to a wide range of healthcare providers from beginners to experts. The current guidelines are filled with the expertise of the working group members, committee members, and directors of the Japanese Society of Intensive Care Medicine (JSICM) and the Japanese Association for Acute Medicine (JAAM). We hope that the guidelines will be used and evaluated by many relevant parties, ultimately leading to improved outcomes for as many patients with sepsis as possible.

BASIC PRINCIPLES AND OVERVIEW OF THE GUIDELINES

Name

The name of the guidelines is the "Japanese Clinical Practice Guidelines for Management of Sepsis and Septic Shock 2024," with the abbreviated designation "J-SSCG 2024" in consideration of the comparison made with the international version.

Objective

Sepsis is a serious disease that affects individuals of all ages, and the present clinical practice guidelines aim to assist healthcare providers in making decisions to improve outcomes in patients with sepsis. The guidelines are mainly intended to be used in medical institutions in Japan, and caution is required when they are used in different medical environments.

Target patients

The guidelines target patients, including children and adults, who have or are suspected of having sepsis or septic shock. These include patients who receive diagnosis and treatment not only in an intensive care unit (ICU) but also in general wards and emergency room (ER). However, because patients with sepsis require high-intensity medical care, the guidelines mainly focus on patients receiving intensive care or its equivalent.

Reflection of patients' values

In order to reflect the values of patients with sepsis and their families, healthcare providers whose family members had sepsis were included in the committee as patient representatives.

Funding for creating the guidelines

The present guidelines were prepared with financial support from the JSICM and the JAAM. None of the members received any compensation for creating the guidelines.

Revision schedule

The present guidelines are scheduled to undergo revision every 4 years, with the next revision scheduled for 2028. Should important findings warranting revision be obtained beforehand, partial revision will be considered.

METHODS FOR CREATING THE GUIDELINES AND INTERPRETATION OF RECOMMENDATIONS

For the definition and diagnosis of sepsis, we adopted the definition of sepsis-3, which is used worldwide.[1]

Important clinical issues

The current revision focused on clinical issues that were considered important in sepsis treatment, and we excluded clinical issues that have already been included in current practice or had too uncertain evidence to create recommendations. Clinical issues were classified into CQ and future research question (FRQ). Additionally, we created recommendations for CQs, according to the GRADE systems or good practice statement (GPS), and provided the information as background questions. We also summarized the background for FRQs.

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Searching, collecting, and integrating evidence through systematic reviews

We conducted a comprehensive literature search for each CQ and extracted randomized controlled trials (RCTs), as well as observational studies as necessary. In principle, evidence was integrated based on the GRADE methodology. The literature search was conducted based on multiple databases, including CENTRAL, PubMed, and Igaku Chuo Zasshi, and we added EMBASE, CINAHL, PsycINFO, and other databases as necessary. When adopting the CQs included in the J-SSCG 2020, we conducted a systematic review of the literature published after the last search. The risk of bias was evaluated according to the method of RoB 2.0[2] for RCTs and that of ROBINS-I for observational studies.[3] Meta-analyses were conducted using RevMan 5. An Evidence to Decision table was created, and recommendations were formulated through discussions at the committee meetings. The modified Delphi method was used for consensus building among the committee members. Each committee member anonymously voted online in an independent manner using a point system between 1 and 9 (1: disagree, 9: agree). The median and disagreement index (DI) of the obtained scores were calculated. Consensus was established when the median was ≥7 and DI was <0.3. For GPS, the median of ≥8 and a DI of <0.20 were set as thresholds for consensus building.

The strength of recommendations based on the GRADE system was classified into the following four categories: "Recommended," "Weakly recommended," "Weakly not recommended," and "Not recommended" (Table 1). The interpretation of certainty of evidence is described in Table 2 and Figures 1–9.

TABLE 1 Interpretation of strong and weak recommendations.

Strength of recommendation	Notation	Example
Strong recommendation for the intervention	1	We recommend –
Weak recommendation for the intervention	2	We suggest –
Weak recommendation against the intervention	2	We suggest against –
Strong recommendation against the intervention	1	We recommend against –

TABLE 2 Interpretation of certainty of evidence.

Certainty of evidence	Notation	Explanation
High	A	High confidence in the estimated value of effects
Moderate	B	Moderate confidence in the estimated value of effects
Low	C	Limited confidence in the estimated value of effects
Very low	D	Little confidence in the estimated value of effects

QUICK REFERENCE LIST OF CQs & ANSWERS

CQ1 Diagnosis and source control

CQ1-1: Definition of sepsis

Answer: Sepsis is defined as a "life-threatening organ dysfunction caused by a dysregulated host response to infection" (*Provision of information for background question*).

CQ1-2: Diagnosis and severity classification of sepsis

Answer: Sepsis is diagnosed when there is an acute increase in the Sequential Organ Failure Assessment (SOFA) score of ≥2 points in the presence of a confirmed or suspected infection. Additionally, septic shock is diagnosed in patients with sepsis when a patient requires vasopressors to maintain a mean arterial pressure of ≥65 mmHg and has a blood lactate level >2 mmol/L (18 mg/dL) despite adequate fluid resuscitation (*Provision of information for background question*).

CQ1-3: What methods are there for early detection of sepsis in general wards and emergency room (ER)?

Answer: Methods for early detection of sepsis in general wards and ER include screening tools, such as quick SOFA (qSOFA) and early warning scores (*Provision of information for background question*).

CQ1-4: When and how are blood culture samples collected for patients suspected with sepsis?

Answer: At least two sets of blood culture samples are collected before antimicrobial administration for patients suspected with sepsis (*Good Practice Statement*).

CQ1-5: When and how are culture specimens other than blood culture samples collected for patients suspected with sepsis?

Answer: Culture specimens are collected from the site of suspected infection before antimicrobial administration for patients suspected with sepsis (*Good Practice Statement*).

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CQ1-6: What are the roles of C-reactive protein (CRP), procalcitonin (PCT), presepsin (P-SEP), and interleukin 6 (IL-6) as biomarkers for sepsis diagnosis?

Answer: CRP, PCT, P-SEP, or IL-6 alone has not been shown to have high diagnostic accuracy for sepsis in general wards, ER, or ICU. Therefore, the diagnosis of sepsis using any specific biomarker is generally considered difficult. The biomarkers are used as supplementary indicators in addition to observation of general conditions (*Provision of information for background question*).

CQ1-7: Are imaging tests performed to identify the source of infection in patients suspected of having sepsis?

Answer: Appropriate imaging tests are conducted according to the suspected disease in patients suspected with sepsis (*Good Practice Statement*).

CQ1-8: When is the source of infection controlled in patients with sepsis?

Answer: The source of infection is controlled as soon as possible after recognition of sepsis (*Good Practice Statement*).

CQ1-9: Which facility is appropriate for managing patients with sepsis who are unresponsive to initial fluid resuscitation?

Answer: Patients with sepsis who are unresponsive to initial fluid resuscitation are managed in a facility capable of providing intensive care (*Good Practice Statement*).

CQ2 Antimicrobial therapy

CQ2-1: Is Gram stain testing useful for selecting empiric antimicrobials for sepsis?

Answer: We suggest using Gram stain testing for selecting empiric antimicrobials for sepsis (GRADE 2C).

CQ2-2: Is the administration of empiric antimicrobials for sepsis started within 1 h after diagnosing sepsis?

Answer: Although antimicrobials should be started as soon as possible after sepsis or septic shock is diagnosed, we suggest against the use of <1 h target time (GRADE 2C).

CQ2-3: How are empiric antimicrobials selected for sepsis?

Answer: Empiric antimicrobials for sepsis are selected for each suspected source of infection by estimating the causative microorganism based on patient background and epidemiology. Rapid microbial diagnostic tests, tissue penetration, and the possibility of resistant bacteria are also assessed (*Provision of information for background question*). (See Data S1 and S2).

CQ2-4. Under what circumstances is carbapenem included in empiric antimicrobials for sepsis?

Answer: Carbapenem is included in empiric antimicrobials for sepsis when an infection is expected to be caused by a microorganism with susceptibility limited to carbapenems, such as extended-spectrum beta-lactamase (ESBL)-producing Enterobacterales, antibiotic-resistant *Pseudomonas aeruginosa*, or *Acinetobacter* spp. (*Provision of information for background question*).

CQ2-5: Under what circumstances are empiric antimicrobials against MRSA or atypical pathogens (such as Candida, viruses, Legionella, Rickettsia, and *Clostridioides difficile*) selected for sepsis?

Answer: Empiric antimicrobials against MRSA or atypical pathogens are selected when an infection is suspected to be caused by each of these microorganisms based on the infection focus, patient background, or microbiological findings for sepsis (*Provision of information for background question*).

CQ2-6: What is used as a reference for adjusting the doses of renally-excreted antimicrobials for sepsis?

Answer: Renal function tests measured at multiple time points, changes in body fluids, as well as the presence of renal replacement therapy and other extracorporeal circulation, are used as references for adjusting the doses of renally-excreted antimicrobials for sepsis (*Provision of information for background question*).

CQ2-7: Is continuous or extended infusion of antimicrobials used for sepsis?

Answers:

We suggest using continuous or extended infusion of β-lactam antimicrobials for sepsis (GRADE 2B).

We suggest against using continuous or extended infusion of glycopeptide antimicrobials for sepsis (GRADE 2C).

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CQ2-8: Is antimicrobial dosage adjusted using therapeutic drug monitoring (TDM) for sepsis?

Answer: We suggest antimicrobial administration using TDM for sepsis (GRADE 2D).

CQ 2-9: Is de-escalation based on culture and susceptibility results performed in antimicrobial therapy for sepsis?

Answer: We suggest applying de-escalation based on culture and susceptibility results performed in antimicrobial therapy for sepsis (GRADE 2C).

CQ2-10: In patients with sepsis receiving empiric antifungal drugs, are antifungal drugs discontinued using β-D glucan as an indicator?

Answer: We suggest the use of β-D glucan as an indicator for the discontinuation of antifungal drugs in patients with sepsis who have been administered empiric antifungal drugs (GRADE 2C).

CQ2-11: Is PCT used as an indicator for discontinuing antimicrobial therapy for sepsis?

Answer: We suggest the use of PCT as an indicator for discontinuing antimicrobial therapy for sepsis (GRADE 2A).

CQ2-12: Is short-term (≤7 days) antimicrobial therapy used for sepsis?

Answer: We suggest applying short-term (≤7 days) antimicrobial therapy for sepsis (GRADE 2C).

CQ3 Initial resuscitation

CQ3-1: What parameters are used to assess tissue hypoperfusion in initial resuscitation for sepsis?

Answer: The measurement of blood lactate level is commonly performed, and the usefulness of capillary refill time (CRT) has also been reported to assess tissue hypoperfusion during initial resuscitation for sepsis (*Provision of information for background question*).

CQ3-2: Are cardiac function and preload evaluated using echocardiography in initial resuscitation for sepsis?

Answer: Cardiac function and preload are evaluated using echocardiography while performing initial resuscitation for sepsis (*Good Practice Statement*).

CQ3-3: What is the target mean arterial pressure (MAP) during initial resuscitation for sepsis?

Answer: We suggest 65 mmHg as the target MAP during initial resuscitation for sepsis (GRADE 2C).

CQ3-4: Which fluid is used for initial resuscitation of sepsis?

Answer: During initial resuscitation for sepsis, we suggest the administration of balanced crystalloid over normal saline (GRADE 2C).

We suggest the administration of isotonic albumin preparations (4–5%) when a patient with sepsis does not respond to standard treatment using crystalloids and requires a large volume of crystalloids (GRADE 2B).

During initial resuscitation for sepsis, we recommend against the administration of synthetic colloids (GRADE 1B).

CQ3-5: How is initial fluid therapy given for patients with sepsis?

Answer: Initial fluids for septic patients with reduced intravascular volume are aimed at optimizing circulating blood volume, and some patients require the administration of at least 30 mL/kg of crystalloid solutions within 3 h. However, there has been caution for harm caused by excessive fluid administration (*Provision of information for background question*).

CQ3-6: Is early administration of vasopressor performed during initial resuscitation for sepsis?

Answer: During initial resuscitation for sepsis with hypotension, we suggest early administration of vasopressor combined with resuscitative fluid therapy (GRADE 2C).

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CQ3-7: Which vasopressor is used as the first-line and second-line drugs in patients with septic shock?

Answer: We suggest using noradrenaline as the first-line vasopressor for septic shock (GRADE 2D), and vasopressin as the second-line vasopressor for septic shock (GRADE 2A).

CQ3-8: Are steroids administered for septic shock?

Answer: We suggest administering low-dose hydrocortisone (200–300 mg/day) to patients with septic shock unresponsive to initial fluid resuscitation and vasopressors for the purpose of recovering from shock (GRADE 2C).

CQ3-9: What is the threshold of hemoglobin level for transfusion in initial resuscitation for septic shock?

Answer: We suggest a hemoglobin level of 7 g/dL as a threshold for transfusion in initial resuscitation for septic shock (GRADE 2C).

CQ3-10: Are β1-adrenoceptor antagonists used for septic patients with persistent tachycardia after initial resuscitation?

Answer: We suggest administering β1-adrenoceptor antagonists for patients with sepsis to manage persistent tachycardia after initial resuscitation (GRADE 2C).

CQ3-11: Is sodium bicarbonate intravenously administered for septic patients with severe metabolic acidosis (pH ≤7.2)?

Answer: We suggest the intravenous administration of sodium bicarbonate for septic patients with severe metabolic acidosis (pH ≤7.2) (GRADE 2C).

CQ3-12: What is the indication for mechanical circulatory support for septic shock?

Answer: There has been insufficient evidence for the effects of mechanical circulatory supports, such as veno-arterial extracorporeal membrane oxygenation (V-A ECMO), intra-aortic balloon pumping, and intracardiac pump catheter (Impella®, Abiomed) for cardiac dysfunction in septic shock, and their indications have not been established (*Provision of information for background question*).

CQ3-13: Is restrictive fluid management provided in septic patients with stable hemodynamics?

Answer: We suggest providing restrictive fluid management in septic patients with stable hemodynamics with monitoring for ischemic organ dysfunction due to hypoperfusion (GRADE 2C).

Remarks: Hypoperfusion can be comprehensively evaluated using skin findings (such as mottling and peripheral cyanosis), vital signs, capillary refill time, lactate levels, or urinary output.

CQ4 Blood purification

CQ4-1: Is polymyxin B-immobilized fiber column (PMX-DHP) used for patients with septic shock?

Answer: We suggest against using PMX-DHP for patients with septic shock (GRADE 2D).

CQ4-2: Is early renal replacement therapy (RRT) performed for septic acute kidney injury (AKI)?

Answer: We suggest against performing early RRT for patients with septic AKI (GRADE 2C).

CQ4-3: Is continuous RRT provided for septic AKI?

Answer: Either continuous or intermittent RRT can be selected as an RRT modality for septic AKI (GRADE 2D).

However, continuous RRT is used for hemodynamically unstable patients (*Good Practice Statement*).

CQ4-4: Is treatment dose increased in RRT for septic AKI?

Answer: We recommend against increasing the RRT dose beyond the international standard dose (20–25 mL/kg/h) for patients with septic AKI (GRADE 1A).

CQ5 Disseminated intravascular coagulation

CQ5-1: What is the diagnostic method for sepsis-induced disseminated intravascular coagulation (DIC)?

Answer: Several diagnostic criteria for DIC in patients with sepsis have been proposed. The Japanese Association for Acute Medicine DIC (JAAM-DIC) and the sepsis-induced coagulopathy (SIC) diagnostic criteria are used to diagnose early DIC and

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to determine treatment initiation. The International Society on Thrombosis and Hemostasis (ISTH) overt DIC diagnostic criteria are used to diagnose progressed DIC and predict mortality (*Provision of information for background question*).

CQ5-2: What are the differential diagnoses for patients with suspected sepsis-induced DIC?

Answer: DIC-like clinical conditions include thrombotic microangiopathy (TMA) and heparin-induced thrombocytopenia (HIT), which require differential diagnosis (*Provision of information for background question*).

CQ5-3: Is antithrombin administered for sepsis-induced DIC?

Answer: We suggest the administration of antithrombin for sepsis-induced DIC (GRADE 2B).

CQ5-4: Is recombinant thrombomodulin administered for sepsis-induced DIC?

Answer: We suggest the administration of recombinant thrombomodulin for sepsis-induced DIC (GRADE 2B).

CQ6 Adjuvant therapy

CQ6-1: Is intravenous immunoglobulin (IVIG) administered for sepsis?

Answer: We suggest against the administration of IVIG for sepsis (GRADE 2C).

CQ6-2: Is high-dose vitamin C therapy used for sepsis?

Answer: We suggest against the use of high-dose vitamin C therapy for sepsis (GRADE 2B).

CQ6-3: What is the target blood glucose level for sepsis?

Answer: We suggest 144–180 mg/dL as a target blood glucose level for sepsis (GRADE 2C).

CQ6-4: Is antipyretic therapy provided to febrile patients with sepsis?

Answer: We suggest against antipyretic therapy for febrile patients with sepsis (GRADE 2C).

CQ6-5: Is stress ulcer prophylaxis performed for patients with sepsis to prevent gastrointestinal hemorrhage?

Answer: We suggest performing stress ulcer prophylaxis for patients with sepsis to prevent gastrointestinal bleeding (GRADE 2D).

CQ6-6: How is the body temperature managed in septic patients with hypothermia?

Answer: Rewarming therapy might be rational when hypothermia-associated circulatory disorders or coagulation abnormalities are observed in septic patients with hypothermia (core body temperature of <35°C). However, caution should be taken as rewarming therapy may cause peripheral vasodilation, resulting in adverse events, such as hypotension (*Provision of information for background question*).

CQ6-7: How is tracheal intubation performed for patients with sepsis?

Answer: Pathophysiological conditions for which tracheal intubation is indicated in patients with sepsis include shock and imbalance between oxygen demand and supply, in addition to airway obstruction and hypoxemia. Because sedatives and analgesics used during tracheal intubation may cause hemodynamic fluctuations, it is important to perform appropriate hemodynamic management, such as preparation of vasopressors (*Provision of information for background question*).

CQ7 Post-intensive care syndrome

CQ7-1: Is early rehabilitation implemented to prevent post-intensive care syndrome (PICS)?

Answer: We suggest conducting early rehabilitation to prevent PICS (GRADE 2D).

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CQ 7-2: Is neuromuscular electrical stimulation used to prevent ICU-acquired weakness (ICU-AW)?

Answer: We suggest using neuromuscular electrical stimulation to prevent ICU-AW (GRADE 2C).

CQ7-3: Is follow-up after ICU discharge be implemented to improve physical, cognitive, and mental functions?

Answer: We suggest conducting follow-up after ICU discharge to improve physical, cognitive, and mental functions (GRADE 2D).

CQ7-4: Is rehabilitation after hospital discharge implemented to improve physical, cognitive, and mental functions?

Answer: We suggest performing rehabilitation after hospital discharge to improve physical, cognitive, and mental functions (GRADE 2C).

CQ8 Patient and family care

CQ 8-1: Is written information provided to the families of critically ill patients?

Answer: We suggest providing information related to intensive care to the families of critically ill patients in written or other forms (GRADE 2C).

CQ 8-2: What is the relaxation of visitation restrictions for families of critically ill patients?

Answer: Relaxation of visitation restrictions for families of critically ill patients include unrestricted visiting hours or numbers of visitors and online visitation. There is an opinion that it may be effective in preventing post-intensive care syndrome family (PICS-F). Its necessity should be considered depending on the situation at one's own facility and individual cases (*Provision of information for background question*).

CQ 8-3: What are the methods for supporting decision-making that respect the value systems and ways of thinking in a patient?

Answer: There are methods of supporting decision-making that respect the values systems and ways of thinking of a patient through repeated discussions at multidisciplinary conferences involving patients and their families. One of the methods proposed is careful estimation through surrogate decision makers (e.g., family members) when the intentions of a patients are unclear. While respecting the intentions of patients, appropriate medical information is provided to patients and their families (*Provision of information for background question*).

CQ 8-4: Is an ICU diary kept for critically ill patients?

Answer: We suggest keeping an ICU diary for critically ill patients (GRADE 2C).

CQ 8-5: Is follow-up after ICU discharge provided to families of critically ill patients to improve their mental health?

Answer: In facilities with well-established systems, we suggest providing follow-ups, such as face-to-face, phone, and online interviews after ICU discharge, to families of critically ill patients to improve their mental health (GRADE 2C).

CQ9 Pediatrics

CQ 9-1: How are empiric antimicrobials selected for pediatric septic shock?

Answer: Antimicrobials for all possible microorganisms are selected, taking into account the organ of infection, setting (community, hospital, or ICU), and patient background (e.g., immune status and antimicrobial prescription history) (*Provision of information for background question*).

CQ 9-2: How is initial fluid therapy administered for pediatric sepsis?

Answer: Methods of administering initial fluid therapy to pediatric sepsis include repeated administration of balanced crystalloid solutions, as a 10–20 mL/kg bolus, while evaluating response to therapy. Clinical findings suggestive of fluid overload or poor response to fluid administration can serve as discontinuing fluid therapy. In particular, attention is paid to the amount and rate of bolus administration in patients complicated by heart failure. We cannot provide information regarding the speed of fluid administration or upper limit of total fluid volume (*Provision of information for background question*).

CQ 9-3: How are vasopressors selected for pediatric patients with septic shock?

Answer: Adrenaline or noradrenaline is used as vasopressors in pediatric patients with septic shock, according to physical findings, hemodynamic parameters, and

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echocardiographic findings (*Provision of information for background question*).

CQ 9-4: What is the route of administering vasopressors for pediatric sepsis?

Answer: Vasopressors are generally administered via the central venous line, as they may cause tissue injury when extravasation occurs. However, vasopressors are administered via a peripheral venous line or intraosseous access at appropriate concentrations for short periods to avoid delays in initiating the administration (*Provision of information for background question*).

CQ 9-5: Are steroids administered to pediatric patients with septic shock who are unresponsive to initial fluid therapy and vasopressors?

Answer: We suggest against routine administration of steroids for pediatric patients with septic shock who are unresponsive to initial fluid therapy and vasopressors (GRADE 2D).

CQ 9-6: What is the optimal hemoglobin level for blood transfusion in pediatric patients with sepsis who have stable hemodynamics?

Answer: We suggest transfusing at a hemoglobin level of 7.0 g/dL in hemodynamically stable pediatric patients with sepsis (GRADE 2C).

CQ 9-7: Is strict blood glucose control performed for pediatric sepsis?

Answer: We suggest against strict blood glucose control for pediatric sepsis (GRADE 2C).

CQ 9-8: What are treatment and support policies centered on critically ill pediatric patients?

Answer: It is necessary to support the decision-making that prioritizes the benefits of affected children and respects the values and wishes of the affected children and their families.

A multidisciplinary team has a role in providing appropriate medical information. Actively creating an environment that allows family members to participate in care and support the decision-making process is essential, especially in pediatric patients (*Provision of information for background question*).

QUICK REFERENCE LIST OF FRQs

FRQ1-1: Do artificial intelligence (AI)-based detection systems for sepsis in the ER and ICU improve prognosis compared to conventional detection systems?

FRQ1-2: Is a tele-ICU system useful for managing patients with sepsis?

FRQ3-1: Is hypertonic albumin solutions (20–25%) used as an initial fluid for septic shock?

FRQ3-2: Is adrenaline added when patients with septic shock have difficulty in maintaining hemodynamics with concomitant use of noradrenaline and vasopressin?

FRQ3-3: Are inotropes used for septic shock patients with decreased cardiac function and tissue hypoperfusion?

FRQ3-4: Is the serum albumin level maintained at 3.0 g/dL using hypertonic albumin solutions (20–25%) after initial resuscitation for septic shock?

FRQ3-5: What is the threshold of hemoglobin levels for transfusion in patients with sepsis who have stable hemodynamics?

FRQ5-1: Are antithrombin and thrombomodulin concomitantly administered for sepsis-induced DIC?

FRQ5-2: Is heparin or heparin analogs administered for sepsis-induced DIC?

FRQ6-1. Is IVIG administered for patients with streptococcal toxic shock syndrome (STSS)?

FRQ7-1: Is the ABCDEFGH bundle implemented to prevent PICS?

FRQ9-1: Is IVIG administered for pediatric sepsis?

CQ1 Diagnosis and source control

CQ1-1: Definition of sepsis

Answer: Sepsis is defined as a "life-threatening organ dysfunction caused by a dysregulated host response to infection" (*Provision of information for background question*).

Rationale

The concept of systemic inflammatory response syndrome (SIRS) was proposed in 1992, in which sepsis was defined as SIRS due to infection (sepsis-1).[4] Such a definition was revised with the aim of creating a definition that better reflects the pathophysiology of sepsis (sepsis-2).[5] However, sepsis-2 had no difference in sensitivity or specificity in sepsis diagnosis compared to sepsis-1, and it did not replace the simple, easy-to-use sepsis-1 definition.[6]

A limitation of the sepsis-1 definition was its low specificity in predicting the progression of organ dysfunction and mortality, despite its high sensitivity.[7] Furthermore, the pathophysiology of sepsis has come to be understood not only as systemic inflammation but also as a complex host response to infection and associated organ dysfunction. From this perspective, the definition of sepsis was revised in the

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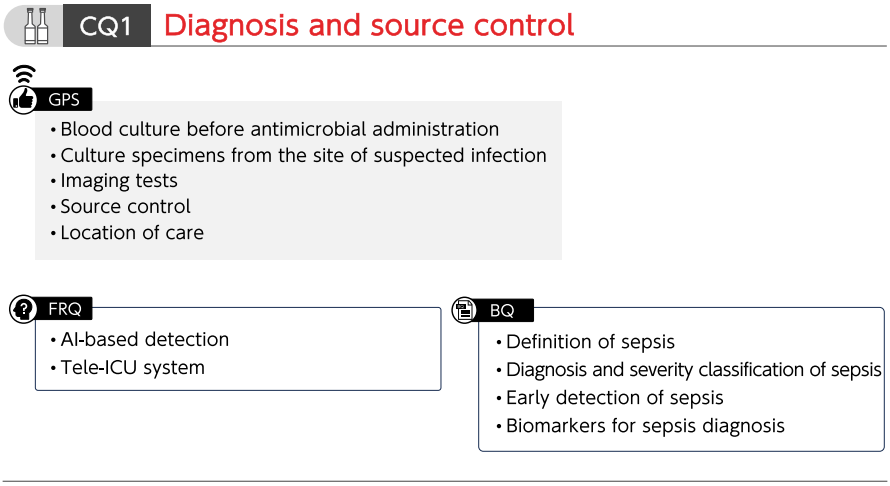
CQ1 Diagnosis and source control
GPS
• Blood culture before antimicrobial administration
• Culture specimens from the site of suspected infection
• Imaging tests
• Source control
• Location of care
FRQ
• AI-based detection
• Tele-ICU system
BQ
• Definition of sepsis
• Diagnosis and severity classification of sepsis
• Early detection of sepsis
• Biomarkers for sepsis diagnosis

FIGURE 1 Summary of recommendations (CQ1 Diagnosis and source control). BQ, background question; CQ, clinical question; FRQ, future research question; GPS, good practice statement; ICU, intensive care unit.

"Third International Consensus Definitions for Sepsis and Septic Shock (sepsis-3)" in 2016.[1] The sepsis-3 was a "life-threatening organ dysfunction caused by a dysregulated host response to infection." Additionally, septic shock was defined as a subset of sepsis in which the underlying circulatory and cellular/metabolic abnormalities profoundly increase the risk of mortality. In the present guidelines, sepsis is defined according to the sepsis-3 definition, as in the J-SSCG 2020.[8,9]

CQ1-2: Diagnosis and severity classification of sepsis

Answer: Sepsis is diagnosed when there is an acute increase in the SOFA score of ≥2 points in the presence of a confirmed or suspected infection. Additionally, septic shock is diagnosed in patients with sepsis when a patient requires vasopressors to maintain a mean arterial pressure of ≥65 mmHg and has a blood lactate level >2 mmol/L (18 mg/dL) despite adequate fluid resuscitation (*Provision of information for background question*).

Rationale

In sepsis-3, the progression of infection-induced organ dysfunction is positioned as an important treatment target,[1] and sepsis diagnostic criteria using the SOFA score[10] has been proposed. In the present guidelines, we adopted the sepsis-3 definition for sepsis and septic shock.

In an ICU, changes in SOFA score are evaluated in patients with confirmed or suspected infections. An acute increase in a SOFA score of ≥2 points is considered the progression of serious organ dysfunction, resulting in a definitive diagnosis of sepsis.

In contrast, SOFA scores may not be easily evaluated outside the ICU. Thus, sepsis-3 proposed sepsis screening using qSOFA.[1] However, due to its low sensitivity for sepsis and hospital mortality, the usefulness of qSOFA as a screening tool is questionable.[11–13] Furthermore, when sepsis is suspected using qSOFA, SOFA score is evaluated to determine sepsis.

Septic shock is the most severe form of sepsis. Sepsis-3 defines septic shock as a condition in which a patient cannot maintain blood pressure with fluid resuscitation alone, requiring vasopressors, such as noradrenaline, and has a blood lactate level of >2 mmol/L (18 mg/dL).

Several issues have been pointed out regarding the sepsis-3 diagnostic criteria for sepsis and septic shock, including the following: (1) due to the low sensitivity of qSOFA for sepsis, there are concerns about screening using qSOFA alone; (2) revision of the SOFA score (revision to SOFA 2.0) is desired worldwide due to its non-uniformness, lack of reproducibility, and inability to be used for evaluating new treatments[14]; (3) the criteria for suspecting infection are unclear[15]; (4) there is a problem of routine measurement of lactate levels; and (5) prompt diagnosis and initiation of treatment are not always integrated.

CQ1-3: What methods are there for early detection of sepsis in general wards and ER?

Answer: Methods for early detection of sepsis in general wards and ER include screening tools, such as qSOFA and early warning scores (*Provision of information for background question*).

Rationale

Early detection of sepsis is important. However, it is challenging to distinguish patients with sepsis from those with other infectious diseases because the pathophysiology is not significantly different. Therefore, screening criteria have been developed focusing on the detection of patients with infectious diseases who have a high risk of mortality and require advanced medical care. Scoring systems, such as SIRS,[4,16] qSOFA,[17] and National Early Warning Score (NEWS)[18] have been evaluated in adult patients. Those

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results suggest that there should be caution when using them independently, and the characteristics and limitations should be well understood. A meta-analysis of 26 studies comparing the mortality prediction ability of SIRS, qSOFA, and NEWS in patients with sepsis showed that SIRS had a high sensitivity (82%) and low specificity (24%), qSOFA had a low sensitivity (46%) and high specificity (82%), and NEWS had a moderate sensitivity (73%) and moderate specificity (52%).[19] For pediatric patients, pediatric early warning score (PEWS) was evaluated as a tool for early detection of status deterioration. A multicenter cluster RCT reported that the use of PEWS reduced the incidence of clinical deterioration events.[20] Additionally, qSOFA has been evaluated in an observational study of pediatric patients suspected of bacterial infections who visited the ER, which reported that an age-adjusted qSOFA had a moderate predictive performance for pediatric ICU admission and mortality (area under the receiver operating curve [AUROC] 0.72).[21]

CQ1-4: When and how are blood culture samples collected for patients suspected with sepsis?

Answer: At least two sets of blood culture samples are collected before antimicrobial administration for patients suspected with sepsis (*Good Practice Statement*).

Rationale

In the treatment of sepsis, identifying the causative pathogen is crucial for appropriate antimicrobial therapy. It is reported that 38–69% of patients with sepsis develop bacteremia.[22,23] Therefore, blood cultures should be collected before antimicrobial administration while paying attention not to delay the start of antimicrobial therapy. This is important because the rate of detecting pathogens decreases after antimicrobial administration, increasing the possibility of not identifying pathogens. Even if antimicrobials have already been administered for conditions like postoperative infection in hospitalized patients, or other reasons, samples for blood culture should be collected before the administration of new antimicrobials. A study reported that microorganisms are detected in approximately 20% of blood culture samples collected after antimicrobial administration.[24]

Regarding the volume of blood for cultures, a sampling volume of 20 mL per set is recommended. Collecting only one set of blood culture results in a low detection rate and difficulty in evaluating contamination. Hence, it is desirable to collect at least two sets of blood cultures, or three sets if possible.[25,26]

Appropriate skin disinfection before the collection of blood culture samples is also important. It is unclear which disinfectant is optimal among 1% chlorhexidine gluconate, povidone-iodine, and 70% alcohol; however, it has been reported that the use of alcohol-containing disinfectants reduces contamination more effectively compared to non-alcohol-containing preparations.[27] Adherence to accurate aseptic techniques to minimize contamination is important.

CQ1-5: When and how are culture specimens other than blood culture samples collected for patients suspected with sepsis?

Answer: Culture specimens are collected from the site of suspected infection before antimicrobial administration for patients suspected with sepsis (*Good Practice Statement*).

Rationale

Blood cultures are the standard method for identifying pathogens in sepsis. However, blood cultures do not have a high positive rate, depending on the situation and source of infection.[22,23] Therefore, we recommend collecting culture specimens other than bloods from the site of suspected infection, based on clinical findings, preferably before the start of antimicrobials.

If pneumonia is suspected, cultures of lower respiratory tract specimens can aid its diagnosis. This is particularly considered for patients with severe pneumonia or those at risk of Methicillin-resistant *Staphylococcus aureus* or *Pseudomonas aeruginosa* infections.[28] For ventilator-associated pneumonia, there is no consensus on whether to use endotracheal aspirate (via blind tracheal suctioning) or bronchoalveolar lavage fluid as a culture specimen. Respiratory symptoms and parameters of patients and the availability of microbiology laboratory at each facility are considered before sampling.[29,30]

When a urinary tract infection is suspected, a urine culture should be obtained before antimicrobial administration to identify the causative bacteria and determine its drug susceptibility. Asymptomatic bacteriuria may occur in older adults and patients with an indwelling urinary catheter. Therefore, antimicrobial therapy should be performed considering physical findings, as well as the results of urinary sediment or blood culture tests.

When bacterial meningitis is suspected, cerebrospinal fluid should be collected before antimicrobial administration if the patient is not contraindicated for a lumbar puncture and has no suspicion of cerebral hernia based on brain computed tomography (CT) or clinical findings. Because delay in antimicrobial administration increases mortality, antimicrobial administration should be prioritized if cerebrospinal fluid collection requires time.[31] Cerebrospinal fluid cultures have a positive rate of 70–80% in untreated patients and ≤50% in patients who have received antimicrobial treatment.[32] Thus, collecting blood cultures before administering antimicrobials can aid in microbial diagnosis when antimicrobials are administered prior to cerebrospinal fluid testing. The positivity of blood cultures was reported to be 75% in patients with community-acquired pneumococcal meningitis.[33]

CQ1-6: What are the roles of CRP, PCT, P-SEP, and IL-6 as biomarkers for sepsis diagnosis?

Answer: CRP, PCT, P-SEP, or IL-6 alone has not been shown to have high diagnostic accuracy for sepsis in general wards, ER, or ICU. Therefore, the diagnosis of sepsis using any specific

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biomarker is generally considered difficult. The biomarkers are used as supplementary indicators in addition to observation of general conditions (*Provision of information for background question*).

Rationale

Clinical diagnosis of sepsis can often be challenging, and a variety of biomarkers are referenced for this purpose. There are four commonly referenced sepsis biomarkers (CRP, PCT, P-SEP, and IL-6), on which many observational studies have been reported. According to the results from meta-analyses, CRP had a sensitivity of 0.75–0.80, specificity of 0.61–0.67, and AUROC of 0.73–0.77,[34,35] PCT had a sensitivity of 0.79–0.80, specificity of 0.77–0.78, and AUROC of 0.85,[34,35] P-SEP had a sensitivity of 0.84, specificity of 0.73–0.76, and AUROC of 0.87–0.88,[36,37] and IL-6 had a sensitivity 0.68–0.72, specificity of 0.73–0.73, and AUROC of 0.79–0.80.[35,38]

Although the reported diagnostic accuracies vary among the biomarkers, none has demonstrated sufficient accuracy to make a diagnosis when used alone. Sepsis is a highly heterogeneous clinical condition depending on the infected organ or underlying disease. In general wards, ER, and ICU, the diagnosis of sepsis using any specific biomarker is generally considered difficult. The biomarkers are used as supplementary indicators in addition to observation of general conditions.

CQ1-7: Are imaging tests performed to identify the source of infection in patients suspected of having sepsis?

Answer: Appropriate imaging tests are conducted according to the suspected disease in patients suspected with sepsis (*Good Practice Statement*).

Rationale

In patients suspected of having sepsis, it is important to evaluate whether there is a source of infection that needs to be controlled. For this purpose, imaging tests, such as ultrasonography, X-ray, CT, and magnetic resonance imaging (MRI) tests are utilized. The most prioritized test should be selected, depending on the suspected infection site. The risk of radiation exposure, as well as the risks associated with the use of a contrast agent, needs to be considered. If a patient has unstable hemodynamics, attention also needs to be paid to any sudden changes in their condition during transportation to an imaging facility.

Table 3 shows common imaging tests according to the source of infection. Contrast-enhanced CT and MRI are used for brain abscess.[39] Ultrasonography and contrast-enhanced CT are used for cervical abscess.[40] A contrast-enhanced CT, chest X-ray, and ultrasonography are used for empyema.[41,42] Ultrasonography is the first choice for infectious endocarditis[43]; however, cardiac CT and positron emission computed tomography with ^{18}F-fluorodeoxyglucose are also used at facilities where the testing is available. Ultrasonography is used for acute abdomen,[44] cholangitis/cholecystitis,[45] and obstructive urinary tract infection,[46] and CT is used in patients whose diagnosis is difficult using ultrasonography. Magnetic resonance imaging and magnetic resonance cholangiopancreatography are applied when a diagnosis cannot be made using CT, despite suspected cholangitis or cholecystitis.[45] For necrotizing soft tissue infection, CT and MRI are applied[47]; however, direct observation of the subcutaneous tissue and fascia through surgical procedures is the most important.

CQ1-8: When is the source of infection controlled in patients with sepsis?

Answer: The source of infection is controlled as soon as possible after recognition of sepsis (*Good Practice Statement*).

TABLE 3 Common imaging tests according to the source of infection.

		Primary imaging tests			
Region	**Suspected source of infection**	**Ultrasonography**	**X-ray**	**CT**	**MRI**
Head and neck	Brain abscess			○ (Contrast-enhanced imaging)	○
	Cervical abscess	○		○ (Contrast-enhanced imaging)	
Chest	Empyema	○	○	○ (Contrast-enhanced imaging)	
	Infective endocarditis	○[a]		CT (Cardiac CT/^{18}F-FDG PET/CT)	
Abdomen	Peritonitis	○		○[b]	
	Cholecystitis/cholangitis	○		○ (Contrast-enhanced imaging)	○
	Obstructive urinary tract infection	○		○	
Other	Necrotic soft tissue infections			○	○

Note: Circles indicate appropriate primary imaging tests.

Abbreviations: ^{18}F-FDG PET/CT, positron emission computed tomography with ^{18}F-fluorodeoxyglucose; CT, computed tomography; MRI, magnetic resonance imaging.

[a]Transesophageal echocardiography is indicated if clinically suspected or in patients with prosthetic valves or other implanted devices.[43]

[b]Contrast-enhanced imaging is recommended for the evaluation of organ ischemia, vascular lesions, and acute pancreatitis.[44]

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Rationale

Appropriate control of infection source is important in the treatment of sepsis and septic shock. As the source of infection is identified, it is promptly controlled after assessing its benefits and complications,[48,49] especially when the infection is unlikely to improve with conventional antimicrobial therapy alone. Even when a patient has a poor general condition due to sepsis or septic shock, control of the infection source is considered if its benefits are judged to outweigh the disadvantages.[50] Exceptionally, for patients with infected pancreatic necrosis, endoscopic or percutaneous drainage is applied when encapsulation is expected (usually after 4 weeks of onset), and if their general condition is maintained with conservative treatment.[51]

In patients with acute pyelonephritis due to urinary tract obstruction, the source of infection is promptly controlled using transurethral stent placement or percutaneous nephrostomy.[52] Timely surgical debridement procedures are important to manage patients with necrotizing soft tissue infection. A meta-analysis of observational studies showed that an early debridement (within 12 h of hospital admission) was associated with reduced mortality.[53] In patients with sepsis suspected of having a catheter-related bloodstream infection, prompt catheter removal is a protective factor of hospital mortality.[54] Empyema is another clinical condition that requires control of the infection source, for which open or percutaneous thoracic drainage is performed.[55,56]

CQ1-9: Which facility is appropriate for managing patients with sepsis who are unresponsive to initial fluid resuscitation?

Answer: Patients with sepsis who are unresponsive to initial fluid resuscitation are managed in a facility capable of providing intensive care (*Good Practice Statement*).

Rationale

Sepsis is a very common clinical condition that can be encountered in any clinical department or medical facility, and its treatment involves a variety of healthcare providers. Patients with sepsis, or those suspected to have sepsis, are occasionally treated in general wards. However, it should be noted that patient outcomes may deteriorate in situations where sufficient medical resources cannot be provided. Therefore, it is critical to evaluate the severity of each patient and select an appropriate setting for care.

The criterion of "sepsis that is unresponsive to initial fluid resuscitation" includes not only septic shock but also persistent hypotension, prolonged disturbance of consciousness, deteriorated respiratory conditions, and poor lactate clearance. The place of treatment should be decided, considering not only the severity but also the required medical resources, prospects for recovery, and patient's preferences.

Japanese nationwide database studies have suggested that ICU admission may be associated with a decreased mortality rate of patients with sepsis.[57,58] An observational study has suggested that treating patients with sepsis in a closed ICU is associated with a decreased hospital mortality rate compared to an open ICU.[59] In pediatric sepsis management, various algorithms have indicated that mechanical ventilation and vasopressors should be started when a patient is determined to be unresponsive to initial fluid resuscitation.[60,61] Therefore, it would be appropriate to make a decision to transition to intensive care management if the patient is "unresponsive to initial fluid resuscitation," and to transfer the patient to a hospital bed capable of providing intensive care or to a nearby facility skilled in pediatric critical care.

FRQ1-1: Do AI-based detection systems for sepsis in the ER and ICU improve prognosis compared to conventional detection systems?

Rationale

Management of sepsis is time-sensitive, and early prediction of sepsis is highly important to reduce mortality. In recent years, AI algorithms have been developed to enable early detection of sepsis with high accuracy, and their usefulness has been investigated.

A systematic review and meta-analysis of diagnostic performance using the Quality Assessment of Diagnostic Accuracy Studies checklist reported that the accuracy of AI-based sepsis diagnosis had an AUROC of 0.68–0.99 for ICU, 0.96–0.98 for in-hospital, and 0.87–0.97 for ER.[62] We performed a systematic review and found only one RCT that assessed the efficacy of AI algorithms. This RCT was conducted at an ICU using a machine learning workflow called "InSight".[63] The mean length of hospital stay was shorter in an intervention group that used InSight (10.3 days) than that in a control group that did not use InSight (13.0 days). Additionally, hospital mortality, which was a secondary endpoint, was lower in the intervention group (9.0%) than that in the control group (21.3%). However, in Japan, InSight has not received the Software as a Medical Device certification as a programmable medical device or undergone any pilot studies. Additionally, early prediction of sepsis using AI may lead to increased use of unnecessary antimicrobials[64] or the occurrence of unknown adverse events. Further studies are needed to evaluate AI-based sepsis detection systems in the future.

FRQ1-2: Is a tele-ICU system useful for managing patients with sepsis?

Rationale

Appropriate and prompt treatment is necessary to improve the prognosis of sepsis. However, due to the limited number

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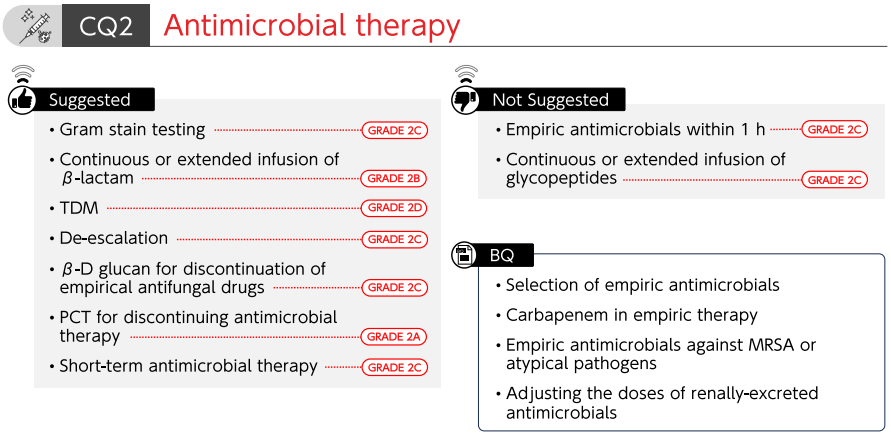
CQ2 Antimicrobial therapy
Suggested
• Gram stain testing GRADE 2C
• Continuous or extended infusion of β-lactam GRADE 2B
• TDM GRADE 2D
• De-escalation GRADE 2C
• β-D glucan for discontinuation of empirical antifungal drugs GRADE 2C
• PCT for discontinuing antimicrobial therapy GRADE 2A
• Short-term antimicrobial therapy GRADE 2C
Not Suggested
• Empiric antimicrobials within 1 h GRADE 2C
• Continuous or extended infusion of glycopeptides GRADE 2C
BQ
• Selection of empiric antimicrobials
• Carbapenem in empiric therapy
• Empiric antimicrobials against MRSA or atypical pathogens
• Adjusting the doses of renally-excreted antimicrobials

FIGURE 2 Summary of recommendations (CQ2 Antimicrobial therapy). BQ, background question; CQ, clinical question; MRSA, methicillin-resistant *Staphylococcus aureus*; TDM, therapeutic drug monitoring.

of specialist physicians, such as intensive care physicians, not all facilities have specialist physicians with enough experiences and knowledge to treat sepsis. "Tele-ICU," which is a medical support system using video/voice calls and computer system networks, is expected to cover the shortage of specialist physicians and ensure standardization of the quality of care.

A systematic review published in 2023 showed that the use of tele-ICU supports may be beneficial in sepsis treatment, particularly in settings where a control group has a low survival rate, and that its effectiveness depends on various hospital-level factors, such as the quality of medical care provided at baseline.[65] However, to date, there have been no high-quality studies evaluating the effectiveness of tele-ICU in the prognosis of patients with sepsis. Future studies are needed to accumulate evidence on the effectiveness of tele-ICU supports in the treatment of patients with sepsis.

CQ2 Antimicrobial therapy

CQ2-1: Is Gram stain testing useful for selecting empiric antimicrobials for sepsis?

Answer: We suggest using Gram stain testing for selecting empiric antimicrobials for sepsis (GRADE 2C).

Rationale

Although drug-resistant bacteria are spreading and becoming more prevalent worldwide, the development of new antimicrobials is on the decline.[66,67] In 2015, the World Health Organization adopted the Global Action Plan, which emphasized the need for appropriate use of broad-spectrum antimicrobials.[68] However, no method of safely limiting the use of broad-spectrum antimicrobials has been established. In recent years, there have also been reports of an association between excessive exposure to broad-spectrum antimicrobials and increased mortality rate.[69,70] Gram stain testing classifies the morphological characteristics of bacteria within minutes, and its results may serve as indicators for the appropriate selection of empiric antimicrobials.

We identified a multicenter RCT (206 patients).[71] As a result of Gram staining-based antimicrobial therapy, a 28-day mortality yielded a risk difference (RD) of 38 fewer per 1000 (95% confidence interval [CI]: 103 fewer to 84 more); clinical response rate yielded an RD of 50 more per 1000 (95% CI: 65 fewer to 180 more); the use of anti-methicillin-resistant *Staphylococcus aureus* (MRSA) drugs yielded an RD of 390 fewer per 1000 (95% CI: 470 fewer to 280 fewer); and the use of antimicrobials having anti-*Pseudomonas aeruginosa* activity yielded an RD of 300 fewer per 1000 (95% CI: 380 fewer to 200 fewer). However, the selection of antimicrobials having antibacterial activity against causative bacteria yielded an RD of 55 fewer per 1000 (95% CI: 138 fewer to 28 more). Based on these findings, we concluded that the balance of effects was probably better for the intervention (Data S3).

Selection of antimicrobials based on Gram staining results requires healthcare providers with the capability of classification by morphological characteristics of bacteria, as well as knowledge of the antimicrobial spectrum. Therefore, it should be noted that its feasibility varies from hospital to hospital.

CQ2-2: Is the administration of empiric antimicrobials for sepsis started within 1 h after diagnosing sepsis?

Answer: Although antimicrobials should be started as soon as possible after sepsis or septic shock is diagnosed, we suggest against the use of <1 h target time (GRADE 2C).

Rationale

The Surviving Sepsis Campaign Guidelines 2021 (SSCG 2021) recommended administering antimicrobials immediately, ideally within 1 h of recognition.[72] However, adhering to the time frame of antimicrobial-administration target of within 1 h may lead to an increase in unnecessary and

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excessive administration of broad-spectrum and multiple antimicrobials.[73] The J-SSCG 2020[8,9] suggested that antibacterial drugs are administered as soon as possible upon identification of sepsis or septic shock, but against using the target time of <1 h (GRADE 2C: certainty of evidence = "low"). Although immediate administration of antimicrobials is recommended, mandating a 1 h timeframe is controversial.

We conducted a meta-analysis of 11 published observational studies.[74–84] Administering antimicrobials within 1 h, hospital mortality yielded an RD of 22 fewer per 1000 (95% CI: 57 fewer to 16 more). The studies included in the meta-analysis did not evaluate the undesirable effects of the intervention. The desirable effects of antimicrobial administration within 1 h were small, and the undesirable effects of the intervention could not be evaluated. These suggest that the balance of effects was neither intervention nor comparator was superior (Data S3).

Although we suggest against using the target time of <1 h for sepsis, the suggestion does not contradict the idea of promptly administering appropriate antimicrobials that cover expected causative pathogens.

CQ2-3: How are empiric antimicrobials selected for sepsis?

Answer: Empiric antimicrobials for sepsis are selected for each suspected source of infection by estimating the causative microorganism based on patient background and epidemiology. Rapid microbial diagnostic tests, tissue penetration, and the possibility of resistant bacteria are also assessed (*Provision of information for background question*). (See Data S1 and S2).

Rationale

Selection of appropriate empiric antimicrobials, along with surgical intervention for the source of infection, is a definitive treatment for sepsis, and is important in improving patient outcomes.[85,86]

According to epidemiological studies in Japan, respiratory tract, intra-abdominal, urinary tract, and soft tissue infections account for 70–90% of sepsis whose source of infection was identified.[87,88] In addition to these sources, catheter-related bloodstream infection is considered.[85–93] In contrast, 28–49% of sepsis patients have unidentified infection foci.[89–94]

External factors, such as healthcare exposure or travel history, and internal factors, such as age, sex, and underlying diseases, can also be considered for estimating causative microorganism. Community-acquired infections are often caused by microorganisms different from those causing healthcare-associated infections, and *Pseudomonas aeruginosa* does not need to be routinely covered. Exposures that serve as risk factors for healthcare-associated infections include invasive procedures, indwelling devices, and prior antimicrobial exposure.

Because the susceptibility of antimicrobials varies, depending on the location, it is important to understand local data, including antibiograms for each region and facility. Tables S1 and S2 show a list of empirical and definitive antimicrobials that are likely to be encountered in sepsis treatment, categorized by susceptibility pattern.

CQ2-4: Under what circumstances is carbapenem included in empiric antimicrobials for sepsis?

Answer: Carbapenem is included in empiric antimicrobials for sepsis when an infection is expected to be caused by a microorganism with susceptibility limited to carbapenems, such as ESBL-producing Enterobacterales, antibiotic-resistant *Pseudomonas aeruginosa*, or *Acinetobacter* spp. (*Provision of information for background question*).

Rationale

Carbapenems are broad-spectrum antimicrobials and often used in empiric therapy, for sepsis and septic shock. However, excessive use of carbapenems carries the risk of increasing carbapenem-resistant bacteria and elevating antimicrobial-related side effects and costs. Selective use of carbapenems in appropriate cases, rather than routine use, is desirable from the perspective of antimicrobial stewardship.

Several studies on sepsis and severe infections have shown that carbapenems and other broad-spectrum β-lactams are equally effective, suggesting a lack of superiority of routine carbapenem use in this setting.[95–101] Although a recent systematic review of 20 RCTs on hospital-acquired pneumonia, including ventilator-associated pneumonia, reported that carbapenems were superior in improving mortality (risk ratio, 0.84; 95% CI: 0.74–0.96),[102] this review showed comparable clinical response rates and an increase in the incidence of resistant bacteria with the use of carbapenems. Excessive use of carbapenems may carry the risk of increasing resistant bacteria. The potential survival benefits of carbapenem use in specific situations should be balanced against the increased risk of antibiotic resistance.

Bacteria for which carbapenems have been shown to have treatment superiority include ESBL-producing Gram-negative bacilli of the Enterobacteriaceae family, and carbapenems may serve as the first-line therapy for these bacteria.[103,104] Additionally, it is reasonable to select carbapenems for cases where the infection is expected to be caused by *Pseudomonas aeruginosa* or *Acinetobacter species* with susceptibility limited to carbapenems. However, such resistant strains are rarely found in Japan.

CQ2-5: Under what circumstances are empiric antimicrobials against MRSA or atypical pathogens (such as Candida, viruses, Legionella, Rickettsia, and *Clostridioides difficile*) selected for sepsis?

Answer: Empiric antimicrobials against MRSA or atypical pathogens are selected when an infection is suspected

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to be caused by each of these microorganisms based on the infection focus, patient background, or microbiological findings for sepsis (*Provision of information for background question*).

Rationale

The use of appropriate antimicrobials is required. Antimicrobials should be carefully selected when specific bacteria (MRSA and *Clostridioides difficile*, *Legionella pneumophila*, Rickettsia), fungi, and viruses are suspected.

MRSA bacteremia is a high risk for mortality.[105] Empiric therapy with glycopeptides is reasonable when MRSA infection is strongly suspected based on the background, especially in critically ill patients. Infection with *Legionella pneumophila* can be considered in patients with pneumonia who have been exposed to contaminated water and have risk factors. If rickettsiosis is suspected based on the patient's background or clinical findings, specimens are collected, and tetracycline or quinolone are started without waiting for the test results. Risk factors for developing *Clostridioides difficile* infection include antimicrobial exposure, antacids use,[106] and advanced age.[107] A study has reported that early and appropriate administration of antifungal drugs for Candida infections reduces the mortality rate.[108] Concomitant use of antifungal drugs with antibacterial agents is acceptable in patients with risk factors for Candida infection.

During the influenza epidemic/pandemic, the administration of anti-influenza drugs is considered if the patient is suspected of having respiratory failure, myocarditis, or encephalitis/encephalopathy.[109] Herpes simplex virus (HSV) type 1 is the most common pathogen of viral encephalitis, and it is an indication for empiric antiviral therapy when encephalitis is suspected.[110] In pregnant women, primary infection with HSV type 2 has a risk of leading to disseminated infection.[111] Cytomegalovirus (CMV) infection can be fatal in immunosuppressed patients. Thus, the amount of CMV in the blood is measured regularly and used as a reference for starting therapy.[112] Additionally, severe acute respiratory syndrome coronavirus 2 infection (COVID-19) should be suspected based on the epidemic/pandemic status and patient's physical findings, followed by testing.

CQ2-6: What is used as a reference for adjusting the doses of renally-excreted antimicrobials for sepsis?

Answer: Renal function tests measured at multiple time points, changes in body fluids, as well as the presence of renal replacement therapy and other extracorporeal circulation, are used as references for adjusting the doses of renally-excreted antimicrobials for sepsis (*Provision of information for background question*).

Rationale

Approximately half of AKI in the ICU are caused by sepsis.[113–117] Dosage reduction of renally-excreted antimicrobials is particularly considered for patients with impaired renal function. Additionally, changes in body fluids and volume of distribution are observed in the early stages of sepsis.

When a patient with sepsis-induced AKI is administered renally-excreted water-soluble antimicrobial drugs or renally-excreted lipid-soluble new quinolones, dosage adjustment is performed according to renal function[118–123] (Table 4). Serum creatinine levels estimated glomerular filtration rate, and estimated creatinine clearance are commonly used as indicators of renal function. However, serum creatinine levels do not accurately reflect true renal function during the acute stage of diseases. Renal function is predicted with reference to fluctuations in serum creatinine levels measured at multiple time points.[124,125]

In contrast, dose adjustment in the early stages of sepsis is considered after understanding the following changes in body fluids[126–132]:

1. Dilution of antimicrobials in plasma and extracellular fluids due to increased Vd. Vd is increased in edema due to capillary leakage, fluid therapy, pleural effusion, body fluid drainage, and decreased protein binding rate due to hypoalbuminemia.
2. Increased cardiac output, increased renal blood flow, and increased renal clearance due to vasodilation (augmented renal clearance)

Concentrations of antimicrobials fluctuate when extracorporeal membrane oxygenation or renal replacement therapy is introduced.[133–145] In renal replacement therapy,

TABLE 4 Types of renally-excreted antimicrobials that require dose adjustment with renal dysfunction.

Type of antimicrobials	Exceptions
β-Lactams	Cefoperazone, Ceftriaxone, Biapenem
Aminoglycosides	
Glycopeptides	
Polypeptides	
New quinolones	Moxifloxacin (oral administration)
Sulfamethoxazole-Trimethoprim	
Fluoropyrimidines	
Triazoles	Itraconazole, Voriconazole, Posaconazole

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ultrafiltration rate and concentrations measured in waste fluids can be used as references for dose adjustment.[146,147] The doses of drugs may be adjusted based on the measured concentrations where possible.[148]

CQ2-7: Is continuous or extended infusion of antimicrobials used for sepsis?

Answers: We suggest using continuous or extended infusion of β-lactam antimicrobials for sepsis (GRADE 2B).

We suggest against using continuous or extended infusion of glycopeptide antimicrobials for sepsis (GRADE 2C).

Rationale

β-Lactams. Beta-lactam antimicrobials are widely used in sepsis treatment. Because β-lactams exhibit a time-dependent antibacterial effect, their continuous administration or extension of infusion time may be beneficial from the perspective of pharmacokinetics/pharmacodynamics (PK/PD). Continuous administration of β-lactam drugs and extended infusion time was suggested in the J-SSCG2020.[8,9]

We conducted a meta-analysis of 17 RCTs.[149–165] As a result of continuous administration or extended infusion time of β-lactam drugs, the mortality yielded an RD of 53 fewer per 1000 (95% CI: 96 fewer to 0), and the clinical response rate yielded an RD of 109 more per 1000 (95% CI: 18 more to 214 more). Furthermore, side effects yielded an RD of 1 fewer per 1000 (95% CI: 23 fewer to 31 more), and the detection of drug-resistant bacteria yielded an RD of 14 fewer per 1000 (95% CI: 58 fewer to 45 more). Thus, we concluded that the balance of effects was probably better for the intervention (Data S3).

No special procedure is required for the continuous administration of antimicrobial agents or the extension of their time of administration. Although a syringe pump is required, this can be relatively performed easily in an ICU and will be well tolerated by healthcare providers. Few facilities routinely perform continuous administration of antimicrobial agents or extended their times of administration, and there may be a need to educate nurses, obtain the cooperation and monitoring of pharmacists, and in-hospital consensus prior to implementation. Furthermore, the time of usage of medical resources needed for continuous administration (e.g., infusion pumps and syringe pumps) will also likely increase.

Glycopeptides. Glycopeptides, such as vancomycin, are widely used for MRSA infection. Because glycopeptides, as with β-lactams, exhibit a time-dependent antibacterial effect, their continuous administration or extended infusion time is considered effective from the perspective of PK/PD. Their blood concentrations need to be kept within a safe range since the side effect of renal damage increases in proportion to the increase in blood concentrations, and there is a possibility of using continuous administration instead of intermittent administration.

We conducted a meta-analysis of three RCTs.[166–168] As a result of continuous administration of glycopeptide drugs or extended infusion time, mortality yielded an RD of 16 more per 1000 (95% CI: 121 fewer to 242 more), and clinical cure yielded an RD of 24 fewer per 1000 (95% CI: 154 fewer to 130 more). However, side effects yielded an RD of 49 fewer per 1000 (95% CI: 107 fewer to 68 more). Considering the relative value of each outcome, we concluded that the balance of effects was probably better for the comparator (Data S3).

CQ2-8: Is antimicrobial dosage adjusted using TDM for sepsis?

Answer: We suggest antimicrobial administration using TDM for sepsis (GRADE 2D).

Rationale

Since the blood concentrations of antimicrobials in patients with sepsis fluctuate due to vascular hyperpermeability or changes in renal blood flow, antimicrobial administration requires dose adjustment, and there have been studies on appropriate designing for the administration of antimicrobials through the measurement of their blood concentrations (i.e., TDM).[118,122,169] Because inappropriate antimicrobial blood concentrations cause treatment failure or organ dysfunction, the clinical question of whether TDM-based treatment strategies improve sepsis outcomes is an important issue.[170–172]

We conducted a meta-analysis of five RCTs that evaluated TDM-based antimicrobial administration, focusing on mortality (five RCTs, 1011 patients)[173–177] and clinical cure (three RCTs, 250 patients).[173,174,176,178] Considering the relative value of each outcome, the net desirable effect yielded an RD of 124 more per 1000 (95% CI: 57 fewer to 304 more). In contrast, no harm was basically expected from performing TDM. Based on these, we concluded that the balance of effects was probably better for the intervention (Data S3).

To measure blood concentrations of drugs, new measurement systems need to be set up with high-performance liquid chromatography or liquid chromatograph mass spectrometer (liquid chromatography with tandem mass spectrometry), making it difficult to introduce TDM. Implementation of TDM is considered especially for patients in whom blood concentrations of antimicrobials are expected to fluctuate.

CQ 2–9: Is de-escalation based on culture and susceptibility results performed in antimicrobial therapy for sepsis?

Answer: We suggest applying de-escalation based on culture and susceptibility results performed in antimicrobial therapy for sepsis (GRADE 2C).

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Rationale

The use of broad-spectrum antimicrobials promotes drug resistance (antimicrobial resistance, AMR), which is a worldwide problem, contributing to rising healthcare costs. De-escalation can be implemented from the perspectives of measures for AMR, infection management, and medical economics if it can be performed safely.

We conducted meta-analyses of one RCT and 17 observational studies. In these analyses, a decrease in overall mortality was considered a desirable effect, although the occurrence of superinfection was considered an undesirable effect. The results from one RCT (116 patients)[179] showed that the mortality yielded an RD of 78 more per 1000 (95% CI: 64 fewer to 335 more; the certainty of evidence: very low), but that with 17 observational studies (4374 patients)[180–196] showed that mortality yielded an RD of 92 fewer per 1000 (95% CI: 121 fewer to 58 fewer; the certainty of evidence: low). The small sample size in the RCT may have led to inconsistency in the results compared with that in the observational studies. Based on these, the desirable effect was assessed to be small. The meta-analysis with one RCT[179] demonstrated that the occurrence of superinfection yielded an RD of 166 more per 1000 (95% CI: 8 more to 539 more). However, we could not perform a meta-analysis with the observational studies,[180–196] as none of the studies evaluated the outcome, based on which the undesirable effect was assessed as unknown. Therefore, we concluded that the balance of effects was probably better for the intervention (Data S3).

The only intervention is a change in antimicrobials, which can be easily implemented in many medical facilities. De-escalation may extend the total duration of antimicrobial therapy,[179] and care should be taken to avoid unnecessary extension of the administration period.[197]

CQ2-10: In patients with sepsis receiving empiric antifungal drugs, are antifungal drugs discontinued using β-D glucan as an indicator?

Answer: We suggest the use of β-D glucan as an indicator for the discontinuation of antifungal drugs in patients with sepsis who have been administered empiric antifungal drugs (GRADE 2C).

Rationale

Because fungal infections, especially candidemia, have a high mortality rate,[198,199] the administration of empiric antifungal drugs is considered for patients with sepsis strongly suspected of having fungal infection. It takes time to make definitive diagnoses of fungal infections, and there are risks of drug-induced adverse events and selection of resistance strains. Therefore, whether antifungal drugs can be safely discontinued once the administration of empiric antifungal drugs has initiated is an important clinical issue.

We conducted a meta-analysis of two RCTs. As a result of β-D glucan-guided antifungal therapy, the duration of antifungal administration yielded a mean difference (MD) of 7.64 days shorter (95% CI: 8.74 shorter to 6.54 shorter),[200,201] and a 28–30-day mortality yielded an RD of 3 more per 1000 (95% CI: 91 fewer to 146 more). The detection of antifungal-resistant candida yielded an RD of 20 more per 1000 (95% CI: 47 fewer to 254 more). Considering the small effect size and wide 95% CI, we observed that there was a high degree of uncertainty and that the undesirable effect was small. Based on these, we concluded that the balance of effects was probably better for the intervention (Data S3).

This CQ examined the discontinuation of empiric antifungal drugs in patients with sepsis using β-D glucan. When a patient is definitively diagnosed with invasive candida infection, antifungal drugs should not be discontinued using only β-D glucan as an indicator. The effectiveness of starting empiric antifungal drugs in patients suspected of having infection with fungi other than Candida is unknown.

CQ2-11: Is PCT used as an indicator for discontinuing antimicrobial therapy for sepsis?

Answer: We suggest the use of PCT as an indicator for discontinuing antimicrobial therapy for sepsis (GRADE 2A).

Rationale

A history of antimicrobial exposure is associated with the emergence of drug-resistant bacteria, and it may increase the risk for secondary sepsis.[202,203] Currently, recommended durations of antimicrobials for each infection have become shorter, but whether they are applicable to sepsis is controversial. In patients with sepsis, decreases in PCT and CRP are associated with decreased mortality risk.[204–206] When making the decision to discontinue antibacterial drugs during sepsis treatment, whether the use of PCT or CRP can shorten the duration of antibacterial drugs without worsening outcomes is an important question.

In the present CQ, we conducted a network meta-analysis (NMA) in the following three groups in order to improve the accuracy of effect estimate; the PCT- and CRP-guided strategies and standard treatment.

The NMA was performed using 16 RCTs.[207–222] Regarding PCT-guided strategy, mortality yielded an RD of 32 fewer per 1000 (95% CI: 53 fewer to 9 fewer), duration of antimicrobial therapy yielded a MD of 2.15 days shorter (95% CI: 2.80 shorter to 1.50 shorter), and recurrence yielded an RD of 7 more per 1000 (95% CI: 14 fewer to 32 more). We concluded that the balance of effects was probably better for the intervention (Data S3).

We did not create a recommendation for the CRP-guided strategy. Regarding the CRP-guided strategy, the duration of antimicrobial therapy yielded a MD of 2.69 days shorter (95% CI: 4.70 shorter to 0.67 shorter). The CRP-guided

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strategy may slightly increase the mortality and recurrence, although it had a wide 95% CI.

CQ2-12: Is short-term (≤7 days) antimicrobial therapy used for sepsis?

Answer: We suggest applying short-term (≤7 days) antimicrobial therapy for sepsis (GRADE 2C).

Rationale

The duration of antimicrobial therapy has been determined for each target organ and causative microorganism, but there is a lack of sufficient scientific basis. Regarding the duration of antimicrobial therapy for various infections, such as pneumonia, there are an increasing number of studies suggesting no difference in mortality rate or clinical cure rate between short- and long-term therapies.[223,224] However, the duration of treatment for sepsis remains unclear. The risk of colonization and proliferation of antimicrobial-resistant bacteria, *Clostridioides difficile*, and fungi increases as the duration of antimicrobial administration becomes longer, which may yield a risk of superinfection. The clinical question of whether the duration of antimicrobial administration can be shortened without worsening patient outcomes is important.

We conducted a meta-analysis of six RCTs.[225–230] Short-term antimicrobial therapy was set as an intervention. A decrease in the detection of drug-resistant bacteria was set as a desirable effect, while a decrease in clinical cure, increase in mortality, and increase in new infection events were set as undesirable effects. The detection of drug-resistant bacteria yielded an RD of 132 fewer per 1000 (95% CI: 166 fewer to 292 more), clinical cure yielded an RD of 24 fewer per 1000 (95% CI: 96 fewer to 63 more), mortality yielded an RD of 5 more per 1000 (95% CI: 23 fewer to 39 more), and new infection events yielded an RD of 26 more per 1000 (95% CI: 20 fewer to 96 more). Considering the relative value of each outcome, we concluded that the balance of effects was probably better for the intervention (Data S3).

Few studies evaluated the short-term antimicrobial therapy for pneumonia, intra-abdominal infections, and bacteremia, and no studies evaluated that of urinary tract infections and cholangitis in critically ill patients. Therefore, this recommendation can serve as a reference for short-term antimicrobial treatment for sepsis caused by pneumonia, intra-abdominal infections, or bacteremia. When short-term therapy is applied, attention should be paid to the risks for recurrence and exacerbation.

CQ3 Initial resuscitation

CQ3-1: What parameters are used to assess tissue hypoperfusion in initial resuscitation for sepsis?

Answer: The measurement of blood lactate level is commonly performed, and the usefulness of CRT has also been reported to assess tissue hypoperfusion during initial resuscitation for sepsis (*Provision of information for background question*).

Rationale

Studies on parameters for timely evaluation of the effectiveness of initial resuscitation for sepsis exist. The J-SSCG 2020 and SSCG 2021 have proposed the lactate level and CRT as such parameters.[8,9,72] Lactate level is included in the criteria for diagnosing septic shock, and it is widely used as an indicator of tissue hypoperfusion. A

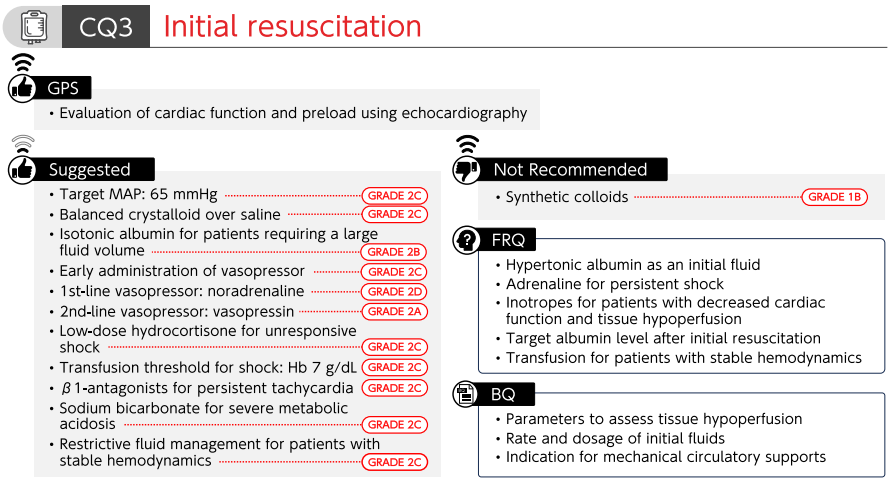
CQ3
Initial resuscitation
GPS
• Evaluation of cardiac function and preload using echocardiography
Suggested
• Target MAP: 65 mmHg GRADE 2C
• Balanced crystalloid over saline GRADE 2C
• Isotonic albumin for patients requiring a large fluid volume GRADE 2B
• Early administration of vasopressor GRADE 2C
• 1st-line vasopressor: noradrenaline GRADE 2D
• 2nd-line vasopressor: vasopressin GRADE 2A
• Low-dose hydrocortisone for unresponsive shock GRADE 2C
• Transfusion threshold for shock: Hb 7 g/dL GRADE 2C
• β1-antagonists for persistent tachycardia GRADE 2C
• Sodium bicarbonate for severe metabolic acidosis GRADE 2C
• Restrictive fluid management for patients with stable hemodynamics GRADE 2C
Not Recommended
• Synthetic colloids GRADE 1B
FRQ
• Hypertonic albumin as an initial fluid
• Adrenaline for persistent shock
• Inotropes for patients with decreased cardiac function and tissue hypoperfusion
• Target albumin level after initial resuscitation
• Transfusion for patients with stable hemodynamics
BQ
• Parameters to assess tissue hypoperfusion
• Rate and dosage of initial fluids
• Indication for mechanical circulatory supports

FIGURE 3 Summary of recommendations (CQ3 Initial resuscitation). BQ, background question; CQ, clinical question; FRQ, future research question; GPS, good practice statement; Hb, hemoglobin; MAP, mean arterial pressure.

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multicenter RCT comparing the use of CRT with lactate level in initial resuscitation for sepsis reported a significant decrease in the SOFA score after 72 h and a trend toward reduced 28-day mortality in the CRT-guided group.[231] Early goal-directed therapy using central venous oxygen saturation ($ScvO_2$) as a parameter did not improve the mortality rate or duration of wearing from mechanical ventilation compared to standard care.[232] Additionally, few studies investigated whether veno-arterial difference in partial pressure of carbon dioxide is useful for initial resuscitation in sepsis.[233] A meta-analysis of 17 RCTs (7729 patients) examining these parameters showed that both lactate-guided and CRT-guided therapy decreased the 90-day mortality compared to management without specific parameters.[234] In contrast, management using $ScvO_2$ may increase the mortality rate compared to those using lactate level.[234] Thus, blood lactate levels and CRT are used as parameters of tissue hypoperfusion in initial resuscitation.

CQ3-2: Are cardiac function and preload evaluated using echocardiography in initial resuscitation for sepsis?

Answer: Cardiac function and preload are evaluated using echocardiography while performing initial resuscitation for sepsis (*Good Practice Statement*).

Rationale

Patients with septic shock can present not only distributive shock associated with peripheral vasodilatation but also hypovolemic or cardiogenic shock. Evaluation using echocardiography, including cardiac function, preload, and fluid responsiveness, may optimize infusion fluid volume during initial resuscitation for sepsis, thereby improving prognosis. However, few RCTs have investigated the assessment using echocardiography in initial resuscitation for sepsis. Previous RCTs had a small sample size, and they did not show the efficacy of echocardiography for decreasing mortality.[235,236] These results were possibly because the experience of ultrasound practitioners was varied, and the optimal thresholds and interventions have not been established. Despite these limitations, we consider that echocardiography is necessary in initial resuscitation for septic shock to examine differential causes of shock other than distributive shock.

CQ3-3: What is the target mean arterial pressure (MAP) during initial resuscitation for sepsis?

Answer: We suggest 65 mmHg as the target MAP during initial resuscitation for sepsis (GRADE 2C).

Rationale

Vasopressors are commonly used in septic patients with hypotension. The risk of hypotension must be balanced against the potential adverse events caused by vasopressors. The SSCG 2021 recommended, with moderate certainty, a MAP of ≥65 mmHg as the initial target blood pressure in adults with septic shock who require vasopressors.[72] However, it is unclear whether maintaining a higher MAP improves outcomes, and we consider this as an important clinical issue.

We conducted a meta-analysis of three RCTs.[237–239] As the effect of setting a higher target MAP of 70–85 mmHg rather than 65 mmHg (60–70 mmHg), the short-term mortality yielded an RD of 12 fewer per 1000 (95% CI: 43 fewer to 24 more), and RRT yielded an RD of 5 fewer per 1000 (95% CI: 33 fewer to 27 more). Serious adverse events (arrhythmia, myocardial injury, extremity necrosis, and mesenteric ischemia) yielded an RD of 16 more per 1000 (95% CI: 6 fewer to 44 more). The desirable effects were trivial, and the undesirable effects were small. Considering the relative value of each outcome and event rates, the benefit of targeting higher MAP was limited, and we concluded that the balance of effects was neither intervention nor comparator was superior (Data S3).

CQ3-4: Which fluid is used for initial resuscitation of sepsis?

Answer: During initial resuscitation for sepsis, we suggest the administration of balanced crystalloid over normal saline (GRADE 2C).

We suggest the administration of isotonic albumin preparations (4–5%) when a patient with sepsis does not respond to standard treatment using crystalloids and requires a large volume of crystalloids (GRADE 2B).

During initial resuscitation for sepsis, we recommend against the administration of synthetic colloids (GRADE 1B).

Rationale

Balanced crystalloids. Large-volume administration of 0.9% sodium chloride (normal saline solution) may cause hyperchloremic metabolic acidosis and increase the risk of AKI.[240] With low-certainty evidence, the SSCG 2021 suggested the use of balanced crystalloids (crystalloids with chloride concentrations similar to that of plasma), rather than normal saline, for adult patients with sepsis or septic shock.[72] We included whether or not to use balanced crystalloids as an important clinical issue.

We analyzed eight publications (seven RCTs, including four cluster RCTs, and a secondary analysis study of one of the RCT).[241–248] Since there was only one study focusing solely on sepsis,[248] the analysis included studies that partially targeted sepsis.

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As the effect of using balanced crystalloids, short-term mortality yielded an RD of 8 fewer per 1000 (95% CI: 18 fewer to 4 more), RRT yielded an RD of 4 fewer per 1000 (95% CI: 12 fewer to 3 more), and hyperkalemia yielded an RD of 1 fewer per 1000 (95% CI: 3 fewer to 4 more). However, the mechanical ventilator yielded an RD of 7 more per 1000 (95% CI: 61 fewer to 88 more). The desirable effects were small, and the undesirable effects were trivial. Therefore, we concluded that the balance of effects was probably better for the intervention (Data S3).

Isotonic albumin solutions (4–5%). We conducted a meta-analysis of four published RCTs.[249–252] As the effect of administering isotonic albumin preparations (4–5%), short-term mortality yielded an RD of 11 fewer per 1000 (95% CI: 94 fewer to 97 more) (four RCTs),[249–252] and serious adverse events (pulmonary edema) yielded an RD of 583 fewer per 1000 (95% CI: 723 fewer to 86 fewer) (one RCT).[249]

Therefore, we observed that the desirable effect was large. Since the studies did not examine any outcomes corresponding to undesirable effects, we found that the undesirable effect was unknown. We concluded that the balance of effects was better for the intervention (Data S3).

Among the RCTs in the meta-analysis, only the SAFE study described the administration of crystalloids prior to allocation,[251] and the dosage of crystalloids prior to the start of albumin solutions remains unclear. However, the administration of crystalloids as an initial fluid is considered to be widely used in daily clinical practice, and we suggest it for patients who are unresponsive to standard treatment using crystalloids and require a large volume of crystalloids.

Synthetic colloids. Synthetic colloids (hydroxyethyl starches) are expected to increase intravascular volume by maintaining colloid osmotic pressure. A recommendation against the administration of synthetic colloids as an initial fluid was made by the J-SSCG 2020[8,9] and SSCG 2021.[72] Whether or not the use of synthetic colloids as an initial fluid for sepsis remains an important issue.

We conducted a meta-analysis of four published RCTs.[253–256] Since there were no studies reporting outcomes that were expected to correspond to desirable effects of the use of synthetic colloids as an initial fluid, we found that the desirable effect was unknown. As for an undesirable effect, the short-term mortality yielded an RD of 9 more per 1000 (95% CI: 25 fewer to 46 more), RRT yielded an RD of 55 more per 1000 (95% CI: 5 more to 118 more), and serious bleeding events yielded an RD of 49 more per 1000 (95% CI: 9 more to 104 more). Considering the relative value of each outcome, the net harm yielded an RD of 131 more per 1000 (95% CI: 1 more to 261 more). We concluded that the balance of effects was probably better for the comparator (Data S3).

CQ3-5: How is initial fluid therapy given for patients with sepsis?

Answer: Initial fluids for septic patients with reduced intravascular volume are aimed at optimizing circulating blood volume, and some patients require the administration of at least 30 mL/kg of crystalloid solutions within 3 h. However, there has been caution for harm caused by excessive fluid administration (*Provision of information for background question*).

Rationale

The J-SSCG 2020 described the necessity of administering at least 30 mL/kg of crystalloid solutions within 3 h during initial fluid therapy for patients with sepsis-induced tissue hypoperfusion and reduced intravascular volume, as well as the importance of avoiding excessive fluid administration with reference to various indicators[8,9] As a strategy of initial fluid therapy, infusion fluids equivalent to 30 mL/kg are becoming widely used in daily clinical practice.[257–259] The harmful effects of excessive fluid administration have also been reported in fluid strategy after the completion of initial fluid therapy.[260]

Kuttab et al. reported that failure to reach an initial fluid resuscitation of 30 mL/kg within 3 h of sepsis onset was significantly associated with an increase in hospital mortality.[261] In large-scale RCTs, such as the ProCESS,[262] ARISE,[263] and ProMISe[264] trials, the volume of initial fluid prior to randomization was approximately 30 mL/kg, which is the volume widely used in daily clinical practice.[257] Subsequent large-scale RCTs on restricted fluid strategies, such as the CLASSIC[258] and CLOVERS[259] trials, also administered 30 mL/kg of resuscitation fluids prior to randomization. A meta-analysis of 15 studies on septic shock reported that excessive fluid balance increased mortality risk by 70%, but focusing on within 3 h of sepsis onset, high-dose administration of fluids led to a decrease hospital mortality.[265] The CLASSIC[258] and CLOVERS[259] trials conducted in recent years showed no difference in the 90-day mortality rate between restricted and unrestricted fluid administration groups.

Based on these, the current standard treatment is the administration of at least 30 mL/kg of crystalloids within 3 h, as an initial resuscitation fluid for septic shock patients with decreased intravascular volume. However, the volume of subsequent fluids continues to be debated.

CQ3-6: Is early administration of vasopressor performed during initial resuscitation for sepsis?

Answer: During initial resuscitation for sepsis with hypotension, we suggest early administration of vasopressor combined with resuscitative fluid therapy (GRADE 2C).

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Rationale

Early administration of vasopressors may avoid excessive fluid administration, thereby improving patient outcomes. In contrast, it may increase adverse events, including ischemic organ dysfunction. The J-SSCG 2020 suggested administering vasopressors simultaneously or in the early stages (within 3 h) of initial fluid resuscitation in patients with sepsis/septic shock who have difficulty in maintaining hemodynamics.[8,9] Since then, several RCTs have been reported, and we considered this as an important clinical issue.

We conducted a meta-analysis of four RCTs.[259,266–268] As the effect of early administration of vasopressor, mortality yielded an RD of 41 fewer per 1000 (95% CI: 80 fewer to 17 more), pulmonary edema yielded an RD of 23 fewer per 1000 (95%CI: 32 fewer to 10 fewer), and AKI yielded an RD of 10 fewer per 1000 (95% CI: 28 fewer to 12 more). In contrast, ischemic organ dysfunction yielded an RD of 4 more per 1000 (95% CI: 2 fewer to 21 more). Considering these results, we concluded that the balance of effects was probably better for early administration of vasopressors (Data S3).

In the CLOVERS study, approximately 30% of enrolled patients were administered vasopressors via peripheral venous lines, and 0.6% of the patients developed extravasation.[259] The occurrence of extravasation was reported in 3.4% (95% CI: 2.5–4.7%) of patients administered vasopressor via peripheral venous lines, but tissue necrosis or limb ischemia were not reported.[269] The administration of vasopressor via peripheral venous lines may be acceptable to avoid delays, but the development of extravasation should be carefully monitored. The most common vasopressor used in those RCTs was noradrenaline.[259,266–268]

CQ3-7: Which vasopressor is used as the first-line and second-line drugs in patients with septic shock?

Answer: We suggest using noradrenaline as the first-line vasopressor for septic shock (GRADE 2D), and vasopressin as the second-line vasopressor for septic shock (GRADE 2A).

Rationale

Noradrenaline. Patients with sepsis often develop hypotension due to venous vasodilation and decreased systemic vascular resistance. Thus, vasopressors are usually administered in initial resuscitation. The J-SSCG 2020[8,9] and the SSCG 2021[72] recommended noradrenaline as the first-line vasopressor. Treatment for hypotension is an important clinical issue during initial resuscitation.

We evaluated four RCTs.[270–273] As the effect of noradrenaline administration, short-term mortality yielded an RD of 21 fewer per 1000 (95% CI: 101 fewer to 69 more), arrhythmia yielded an RD of 124 fewer per 1000 (95% CI: 176 fewer to 11 fewer), RRT yielded an RD of 1 more per 1000 (95% CI: 21 fewer to 31 more); and organ ischemia (limb and intestinal tract) yielded an RD of 2 more per 1000 (95% CI: 13 fewer to 17 more).

Considering the relative value of each outcome, the net benefit yielded an RD of 312 more per 1000 (95% CI: 7 more to 617 more), and we concluded that the balance of effects was better for the intervention (Data S3).

Noradrenaline + vasopressin. A combination vasopressor therapy is considered in some patients, whose blood pressure cannot be maintained even with the use of noradrenaline. The present guidelines included this as an important clinical issue and evaluated the evidence for combination therapy with vasopressin, which is frequently used as the second-line vasopressor.

We conducted a meta-analyses of five RCTs.[274–278] As the effect of using vasopressin in addition to the noradrenaline, short-term mortality yielded an RD of 21 fewer per 1000 (95% CI: 65 fewer to 31 more), mesenteric ischemia yielded an RD of 7 fewer per 1000 (95% CI: 19 fewer to 16 more), and RRT yielded an RD of 115 fewer per 1000 (95% CI: 191 fewer to 0). Meanwhile, acute coronary syndrome yielded an RD of 8 more per 1000 (95% CI: 101 fewer to 69 more). Considering the relative value of each outcome, the net benefit yielded an RD of 178 more per 1000 (95% CI: 3 more to 353 more). Therefore, we concluded that the balance of effects was probably better for the intervention (Data S3).

No analyses were conducted in a subgroup that was more likely to obtain the beneficial effects of vasopressin, as well as a subgroup that was more likely to obtain its harmful effects. The effectiveness of using vasopressin for septic shock with reduced cardiac function has not been investigated.

CQ3-8: Are steroids administered for septic shock?

Answer: We suggest administering low-dose hydrocortisone (200–300 mg/day) to patients with septic shock unresponsive to initial fluid resuscitation and vasopressors for the purpose of recovering from shock (GRADE 2C).

Rationale

In patients with septic shock unresponsive to initial fluid resuscitation and vasopressors, relative adrenal insufficiency should be considered as the cause of persistent shock. Steroids are expected to lead to recovery from shock because they restore relative adrenal function, suppress inflammatory responses, exert vasoconstrictive effects, and improve responsiveness to vasopressors. In

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contrast, steroids may suppress immune function and increase the risk of infections, gastrointestinal hemorrhage, and hyperglycemia.

We conducted a meta-analysis of 11 RCTs.[275,279–288] The steroid used in all of the RCTs was low-dose hydrocortisone (200–300 mg/day). As a result of the administration of low-dose hydrocortisone, short-term mortality yielded an RD of 12 fewer per 1000 (95% CI: 40 fewer to 18 more), recovery from shock yielded an RD of 60 more per 1000 (95% CI: 30 fewer to 164 more), and the duration of recovery from shock yielded an MD of 1.6 days shorter (95% CI: 2.8 days shorter to 0.4 days shorter). In contrast, serious adverse events yielded an RD of 9 more per 1000 (95% CI: 26 fewer to 54 more), secondary infections yielded an RD of 10 more per 1000 (95% CI: 10 fewer to 31 more), and gastrointestinal hemorrhage yielded an RD of 12 more per 1000 (95% CI: 16 fewer to 55 more). Considering these results, we concluded that the balance of effects was probably better for the administration of low-dose hydrocortisone (Data S3).

Among the included 11 RCTs,[275,279–288] hydrocortisone was administered intermittently in eight RCTs and continuously in three RCTs. Regarding blood glucose management, continuous administration reduced the workload needed to maintain tight blood glucose control,[289] although it was reported to prolong the duration of hyperglycemia.[290] Regarding the method of hydrocortisone dose reduction, some RCTs gradually decreased its dose, while others interrupted the dose. The duration of hydrocortisone administration was 5–12 days.

CQ3-9: What is the threshold of hemoglobin level for transfusion in initial resuscitation for septic shock?

Answer: We suggest a hemoglobin level of 7 g/dL as a threshold for transfusion in initial resuscitation for septic shock (GRADE 2C).

Rationale

The J-SSCG 2020 and SSCG 2021 suggested starting blood transfusion at a hemoglobin level of <7 g/dL during initial resuscitation for patients with septic shock.[8,9,72] However, maintaining relatively high hemoglobin levels for shock may improve tissue hypoxia and reduce ischemic organ dysfunction. We compared management using higher and lower hemoglobin levels as a threshold of blood transfusion for septic shock.

We performed a meta-analysis of three RCTs.[291–293] All of the RCTs adopted a hemoglobin of 9 and 7 g/dL as higher and lower thresholds for transfusion, respectively. As a result of using a higher threshold, the mortality yielded an RD of 20 fewer per 1000 (95% CI: 99 fewer to 69 more). In contrast, serious adverse events yielded an RD of 3 more per 1000 (95% CI: 1 fewer to 113 more), and ischemic organ dysfunction yielded an RD of 1 more per 1000 (95% CI: 23 fewer to 38 more) (Data S3).

The balance of effects was probably better for a higher threshold of hemoglobin level for blood transfusion. However, a meta-analysis similar to this CQ (although there was no improvement in patient-centered outcomes) highlighted that opportunities for blood transfusion increased by 32.8% and that the use of blood transfusion increased by 2.45 units in a liberal transfusion threshold (9 g/dL) group.[294] Considering these results, the threshold of hemoglobin for transfusion for septic shock can be set at 7 g/dL. However, higher hemoglobin levels may be preferred in patients with a history of hyperhemoglobinemia due to chronic hypoxemia, concomitant hemorrhagic shock, concomitant organ ischemia (such as myocardial infarction), and expected hemorrhage due to surgical procedures.

CQ3-10: Are β1-adrenoceptor antagonists used for septic patients with persistent tachycardia after initial resuscitation?

Answer: We suggest administering β1-adrenoceptor antagonists for patients with sepsis to manage persistent tachycardia after initial resuscitation (GRADE 2C).

Rationale

Tachycardia and catecholamine administration are factors associated with poor prognosis in sepsis.[295,296] In patients with septic shock, the use of β1-adrenoceptor antagonists is considered to manage tachycardia. However, β1-adrenoceptor antagonists may worsen hemodynamics, and their effectiveness has not been established.

We performed a meta-analysis of four RCTs.[297–300] As a result of administering β1-adrenoceptor antagonists, the short-term mortality yielded an RD of 206 fewer per 1000 (95% CI: 271 fewer to 130 fewer), and arrhythmia yielded an RD of 160 fewer per 1000 (95% CI: 213 fewer to 46 fewer). Meanwhile, serious adverse events yielded an RD of 3 more per 1000 (95% CI: 62 fewer to 184 more). Considering these results, we concluded that the balance of effects was probably better for administering β1-adrenoceptor antagonists.

Recently, an RCT was published and demonstrated that the administration of landiolol might increase the 28-day mortality rate (37.1% vs. 25.4%, $p = 0.16$), resulting in early termination of the trial.[301] In patients with septic shock who were administered landiolol, noradrenaline was administered at a higher dose of approximately 0.1 μg/kg/min and with a longer duration of approximately 1 day compared to those without landiolol. When we performed a meta-analysis of five RCTs, including this new RCT,[297–301] the balance of effects was still probably better for administering β1-adrenoceptor antagonists (Data S3). However, β1-adrenoceptor antagonists should be administered under careful monitoring of hemodynamics, as they may decrease cardiac output, lower blood pressure, and worsen tissue hypoperfusion.

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CQ3-11: Is sodium bicarbonate intravenously administered for septic patients with severe metabolic acidosis (pH ≤7.2)?

Answer: We suggest the intravenous administration of sodium bicarbonate for septic patients with severe metabolic acidosis (pH ≤7.2) (GRADE2C).

Rationale

Patients with sepsis often develop acute metabolic acidosis, and sodium bicarbonate is used for its correction. However, whether the administration of sodium bicarbonate for severe metabolic acidosis leads to improved outcomes is unclear and controversial. With low-certainty evidence, the SSCG 2021 stated that "For adults with septic shock and hypoperfusion-induced lactic acidemia, we suggest against using sodium bicarbonate therapy to improve hemodynamics or to reduce vasopressor requirements".[72]

Our analysis included four published studies[302–305] (three RCTs[302,304,305]), as well as a secondary analysis study[303] of one of the RCTs. Outcomes were extracted from only one study.[302] Short-term mortality yielded an RD of 91 fewer per 1000 (95% CI: 172 fewer to 11 more), new-onset organ failure yielded an RD of 69 fewer per 1000 (95% CI: 152 fewer to 28 more), and RRT yielded an RD of 165 fewer per 1000 (95% CI: 242 fewer to 72 fewer). In contrast, severe metabolic adverse events requiring treatment intervention yielded an RD of 15 more per 1000 (95% CI: 57 fewer to 118 more). Considering the relative value of each outcome, we concluded that the balance of effects was probably better for the intervention (Data S3).

CQ3-12: What is the indication for mechanical circulatory support for septic shock?

Answer: There has been insufficient evidence for the effects of mechanical circulatory supports, such as V-A ECMO, intra-aortic balloon pumping, and intracardiac pump catheter (Impella®, Abiomed) for cardiac dysfunction in septic shock, and their indications have not been established (*Provision of information for background question*).

Rationale

Patients with septic shock may present not only with distributive shock but also with cardiogenic shock due to sepsis-induced myocardial dysfunction (SIMD).[306,307] In those patients, the incidences of left ventricular systolic, left ventricular diastolic, and right ventricular dysfunctions were reported to be 23–63%,[308–311] 37–68%,[309,310] and 35–48%,[310,312] respectively, all of which may be associated with mortality.[309–312]

Few clinical trials have been reported on the effects of mechanical circulatory support in septic shock patients with SIMD. Twenty-eight-day survival rate in septic shock patients receiving intra-aortic balloon pumping was reported as approximately 30%.[313] In some case series and observational studies using V-A ECMO, survival rates varied widely among studies between 15 and 90%.[314–319] A meta-analysis of the prognosis of patients with septic shock who received V-A ECMO reported an hospital survival rate of 36%.[320] The effect of Impella® in patients with SIMD has also been evaluated insufficiently, with only a few case reports reported.[321,322] Therefore, there has been insufficient evidence on the effectiveness of mechanical circulatory supports in septic shock patients, and their indications have not been established.

Sepsis-induced myocardial dysfunction is a reversible clinical condition, and mechanical circulatory support may be used in septic patients with poor cardiac dysfunction if their hemodynamics cannot be maintained with inotropes. An appropriate device can be selected based on the assessment of the severity of shock-induced organ dysfunction, degree of cardiac dysfunction, and risk of complications. It is desirable that mechanical circulatory supports are provided at an experienced facility.

CQ3-13: Is restrictive fluid management provided in septic patients with stable hemodynamics?

Answer: We suggest providing restrictive fluid management in septic patients with stable hemodynamics with monitoring for ischemic organ dysfunction due to hypoperfusion (GRADE 2C).

Remarks: Hypoperfusion can be comprehensively evaluated using skin findings (such as mottling and peripheral cyanosis), vital signs, capillary refill time, lactate levels, or urinary output.

Rationale

Both fluid overload and underload are associated with increased mortality in patients with sepsis.[323] Restrictive fluid management may improve prognosis by reducing organ congestion, but increase adverse events, including ischemic organ dysfunction.

We performed a meta-analysis of eight RCTs.[258,259,267,324–327] As a result of restrictive fluid management, 90-day mortality yielded an RD of 6 fewer per 1000 (95% CI: 34 fewer to 23 more), AKI or use of RRT yielded an RD of 19 fewer per 1000 (95% CI: 37 fewer to 5 more), and serious adverse events yielded an RD of 8 fewer per 1000 (95% CI: 28 fewer to 16 more). Based on these findings, we concluded that the balance of effects was probably better for restrictive fluid management (Data S3). Additionally, another systematic review and meta-analysis similar to our analysis showed no significant difference in any outcomes between higher and lower fluid volume managements.[327] Although sensitivity analyses were performed regarding the risk of bias, severity of illness, protocol, timing of intervention, and definition of sepsis, no significant difference was observed in any subgroups.

Restrictive fluid management is expected to reduce organ congestion associated with excessive fluids. However,

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in most of the RCTs included in our analysis, fluids of at least 20–30 mL/kg had already been administered before the study enrollment.[258,324,326–329] That means fluid volume administered during initial resuscitation was not restricted. If there is a concern about ischemic organ dysfunction due to hypoperfusion, resuscitation fluid should not be hesitated. Evaluation of fluid responsiveness is required to avoid excessive fluids.

FRQ3-1: Is hypertonic albumin solutions (20–25%) used as an initial fluid for septic shock?

Rationale

The optimal albumin concentrations, isotonic (4–5%) or hypertonic (20–25%), for initial resuscitation in septic shock remain controversial. The clinical benefit of using hypertonic albumin as an initial resuscitation fluid in septic shock is uncertain.

There are two types of albumin solutions: isotonic (with a concentration close to that in human plasma: 4–5%) and hypertonic (with a high concentration: 20–25%). Experimental data and observational studies have suggested that hypertonic albumin solutions may be more effective than isotonic solutions in increasing intravascular volume and may enable resuscitation with smaller fluid volumes. In contrast, there is a possibility that they may not achieve the theoretical effect of increasing intravascular volume in patients with significant capillary leakage, such as septic shock. Additionally, rapid administration of hypertonic albumin solutions may induce a hyperosmolar state, leading to a decreased glomerular filtration rate.

The RCTs investigating the use of hypertonic albumin solutions for initial fluids for septic shock include the ERASS and ALPS trials. The ERASS trial ($n=792$) showed no significant difference in the 28-day mortality between 20% albumin and 0.9% saline (24.1% vs. 26.3%), with comparable incidence rates of kidney failure.[330] In the ALPS trial ($n=100$), there was no significant difference in the 28-day mortality between 20% albumin and crystalloids (58% vs. 56%).[331]

Further RCTs are needed to investigate whether the use of hypertonic albumin solutions reduces the volume of initial fluids for septic shock or whether it improves septic shock outcomes.

FRQ3-2: Is adrenaline added when patients with septic shock have difficulty in maintaining hemodynamics with concomitant use of noradrenaline and vasopressin?

Rationale

The SSCG 2021 recommended the addition of adrenaline to achieve the target mean blood pressure during the initial resuscitation for sepsis when concomitant use of noradrenaline and vasopressin does not achieve a sufficient pressor effect after sufficient infusion fluid therapy,[72] although this has not been investigated in any RCT. Under the use of high-dose noradrenaline, α1 receptors may already be saturated and downregulated. The administration of adrenaline is expected to exert effects as an inotrope in patients with decreased cardiac function, rather than the effects on α1 receptor. However, it may increase adverse events, such as organ ischemia associated with α stimulation effect and arrhythmia associated with β stimulation effect.[332]

Future RCTs will investigate the usefulness of adrenaline, including the timing and dosage.

FRQ3-3: Are inotropes used for septic shock patients with decreased cardiac function and tissue hypoperfusion?

Rationale

Approximately 40% of patients with septic shock are complicated by a cardiac dysfunction called SIMD, and its association with aggravation of the disease has been suggested.[333,334] In order to maintain tissue perfusion in patients with SIMD-complicated septic shock, inotropes, dobutamine, and adrenaline, in addition to vasopressors, have been used. The SSCG 2021 recommended the concomitant use of noradrenaline and dobutamine, or the administration of adrenaline alone for septic shock patients with decreased cardiac function, who exhibit persistent tissue hypoperfusion despite maintaining appropriate fluid resuscitation and maintained arterial pressure, although it is not based on sufficient evidence.[72]

Inotropes include dobutamine, adrenaline, and calcium (Ca) sensitizers. The SSCG 2021 suggested against the use of Ca sensitizers and did not mention PDE III inhibitors.[72] At the time of publication of the SSCG 2021, there were no RCTs comparing dobutamine, adrenaline, and PDE III inhibitors. Regarding the use of Ca sensitizers, three RCTs have been conducted, and no association with mortality was found in a group using Ca sensitizers compared to a placebo group. However, a multicenter RCT study suggested that the use of Ca sensitizers hindered successful weaning from invasive mechanical ventilation and increased supraventricular arrhythmia.[335]

Since the publication of the SSCG 2021, there have been no new RCTs on the use of inotropes in patients with septic shock complicated by decreased cardiac function.

FRQ3-4: Is the serum albumin level maintained at 3.0 g/dL using hypertonic albumin solutions (20–25%) after initial resuscitation for septic shock?

Rationale

Albumin has various properties, including increasing intravascular volume, regulating colloid osmotic pressure, binding and transporting different molecules, exerting anti-inflammatory and antioxidant effects, and regulating nitric

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oxide metabolism. Hypoalbuminemia is associated with poor prognosis in critically ill patients, and the aforementioned effects of albumin may be lost in patients with sepsis.

Hypertonic albumin solutions may correct hypoalbuminemia, maintain colloid osmotic pressure, reduce edema, and improve outcomes in patients with septic shock. However, the clinical benefit of maintaining serum albumin levels in patients with septic shock using hypertonic albumin solutions remains uncertain.

In the ALBIOS trial, patients administered 20% albumin solutions and crystalloids to maintain serum albumin levels ≥3.0 g/dL were compared with those administered crystalloids alone. The study showed no significant difference in the 28- and 90-day mortality.[336] However, a subgroup analysis suggested that the maintenance of serum albumin levels may reduce the 90-day mortality in patients with septic shock ($n = 1121$) (risk ratio: 0.87 [95% CI: 0.77–0.99]). Two ongoing RCTs, the ARISS[337] and ALBIOSS-BAL[338] trials, tested this hypothesis after initial resuscitation for septic shock.

FRQ3-5: What is the threshold of hemoglobin levels for transfusion in patients with sepsis who have stable hemodynamics?

Rationale

Tissue hypoxia accompanying anemia is a clinically important issue. Blood transfusion is performed to treat and prevent tissue hypoxia, but increasing blood transfusion is associated with the risk of allergies, infection, blood transfusion, transfusion-associated circulatory overload, and transfusion-related acute lung injury. The threshold of hemoglobin level for transfusion in patients with sepsis who have stable hemodynamics has not been established.

In a RCT conducted by Hebert et al.,[339] 838 critically ill patients with a hemoglobin of <9.0 g/dL were randomly allocated into the following two groups; (1) those that maintained hemoglobin of 7.0–9.0 g/dL (restricted transfusion group; 418 patients); and (2) those that maintained hemoglobin of 10.0–12.0 g/dL with a blood transfusion threshold of hemoglobin 10.0 g/dL (unrestricted transfusion group; 420 patients). No significant difference was observed in the 30-day mortality, which was the primary endpoint (restricted transfusion group, 18.7% vs. unrestricted transfusion group, 23.3%; $p = 0.11$), but hospital mortality was significantly lower in the restricted transfusion group (22.3% vs. 28.1%, $p = 0.05$). A subgroup analysis in patients with septic shock showed no significant difference in the 30-day mortality (restricted transfusion group 22.8% vs. unrestricted transfusion group 29.7%, $p = 0.36$).

No clinical trials have been conducted to investigate the threshold of hemoglobin levels for the initiation of blood transfusion in patients with sepsis who have no signs of shock or have recovered from shock. Clinical trials investigating this question are warranted.

CQ4 Blood purification

CQ4-1: Is PMX-DHP used for patients with septic shock?

Answer: We suggest against using PMX-DHP for patients with septic shock (GRADE 2D).

Rationale

Direct hemoperfusion with PMX-DHP is used for endotoxin adsorption. The J-SSCG 2020 suggested against PMX-DHP for septic shock,[8,9] but the effectiveness of PMX-DHP remains controversial.

We conducted a meta-analysis of four RCTs.[340–343] With regard to the desirable effects of PMX-DHP, mortality yielded a RD of 37 fewer per 1000 (95% CI: 134 fewer to 110 more), and organ dysfunction score yielded a standardized mean difference (SMD) of 0.49 lower (95% CI: 1.2 lower to 0.21 higher). With regard to the undesirable effects of PMX-DHP, complications, such as hemorrhage and in-circuit coagulation, yielded an RD of 216 more per 1000 (95% CI: 91 fewer to 1000 more), vasopressor-free days yielded a MD of 1.8 days shorter (95% CI: 4.1 days

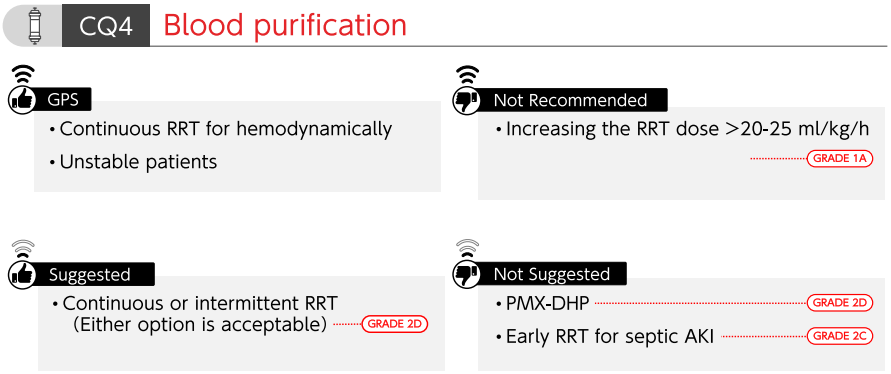

FIGURE 4 Summary of recommendations (CQ4 Blood purification). AKI, acute kidney injury; CQ, clinical question; GPS, good practice statement; PMX-DHP, polymyxin B-immobilized fiber column; RRT, renal replacement therapy.

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shorter to 0.5 days longer). The desirable effects were trivial, and the undesirable effects were large. Thus, we concluded that the balance of effects was probably better for the comparator (Data S3).

Further evidence will be accumulated in future studies, including the currently ongoing RCT (the TIGRIS trial).[344]

CQ4-2: Is early RRT performed for septic AKI?

Answer: We suggest against performing early RRT for patients with septic AKI (GRADE 2C).

Rationale

Patients with septic AKI have higher severity of AKI, requirement of RRT, and mortality rates than those with non-septic AKI.[345] However, there are no clear standards on the timing of starting RRT in septic patients with AKI. In 2020, a large-scale RCT (the STARRT-AKI trial) was reported.[346] In the present guidelines, "early" was defined as AKI stage 2/3 or within 12 h fulfilling inclusion criteria.

We conducted a meta-analysis of four RCTs.[346–349] With regard to the desirable effects of early RRT, dialysis dependence yielded an RD of 12 fewer per 1000 (95% CI: 40 fewer to 70 more), and hemorrhagic complications yielded an RD of 5 fewer per 1000 (95% CI: 12 fewer to 8 more). With regard to the undesirable effects, mortality yielded an RD of 8 more per 1000 (95% CI: 23 fewer to 38 more). Thus, we concluded that the balance of effects was unknown (Data S3).

The actual timing of starting RRT may vary, depending not only on medical aspects but also on the availability of RRT equipment and human resources of each facility. When performing RRT, clinical situation, such as medical resources and the will of patients are considered.

CQ4-3: Is continuous RRT provided for septic AKI?

Answer: Either continuous or intermittent RRT can be selected as an RRT modality for septic AKI (GRADE 2D).

However, continuous RRT is used for hemodynamically unstable patients (*Good Practice Statement*).

Rationale

Renal replacement therapy is an essential life support for patients with advanced septic AKI. RRT is classified into continuous RRT (CRRT) and intermittent RRT (IRRT). The J-SSCG 2020 [8,9] stated that CRRT should be selected for hemodynamically unstable patients and that either CRRT or IRRT can be selected for patients with stable hemodynamics. Whether to use CRRT or IRRT depends not only on the clinical condition but also on the experience and healthcare-providing system of each facility.

We conducted a meta-analysis of five published RCTs[350–354] With regard to the desirable effect of CRRT, hemorrhagic complications yielded an RD of 3 fewer per 1000 (95% CI: 29 fewer to 46 more). With regard to the undesirable effects, mortality yielded an RD of 38 more per 1000 (95% CI: 49 fewer to 136 more), and dialysis dependence yielded an RD of 4 more per 1000 (95% CI: 38 fewer to 106 more). We concluded that the balance of effects was better for IRRT (Data S3). However, we suggest that either continuous or intermittent RRT can be selected, considering both are widely used in clinical settings. An observational study stated that CRRT is generally selected for patients with unstable hemodinamics.[355]

CQ4-4: Is treatment dose increased in RRT for septic AKI?

Answer: We recommend against increasing the RRT dose beyond the international standard dose (20–25 mL/kg/h) for patients with septic AKI (GRADE 1A).

Rationale

In the provision of RRT for patients with septic AKI, increasing the dialysis and filtration dose has been expected to improve prognosis. Approximately 25 mL/kg/h is considered the standard prescribed dose internationally. Setting the prescribed dose with the highest treatment effect for septic AKI is an important issue for improving prognosis.

We performed a meta-analysis of three published RCTs.[356–358] Since the desirable effect of increasing the treatment dose (35–40 mL/kg/h) was not found in the meta-analysis, we assessed that the desirable effect was unknown. With regard to the undesirable effects, mortality yielded an RD of 26 more per 1000 (95% CI: 9 fewer to 64 more), dialysis dependence yielded an RD of 68 more per 1000 (95% CI: 51 fewer to 226 more), and complications (hypophosphatemia) yielded an RD of 124 more per 1000 (95% CI: 4 more to 286 more). Thus, we concluded that the balance of effects was better for the comparator (Data S3).

The RRT dose used in the RCTs of this meta-analysis was 20–25 mL/kg/h.[356–358] The dose approved by Japanese health insurance is 15 mL/kg/h. The efficacy of RRT with the lower dose is unclear.

CQ5 Disseminated intravascular coagulation

CQ5-1: What is the diagnostic method for sepsis-induced DIC?

Answer: Several diagnostic criteria for DIC in patients with sepsis have been proposed. The JAAM-DIC and the SIC diagnostic criteria are used to diagnose early DIC and to determine treatment initiation. The ISTH overt DIC diagnostic

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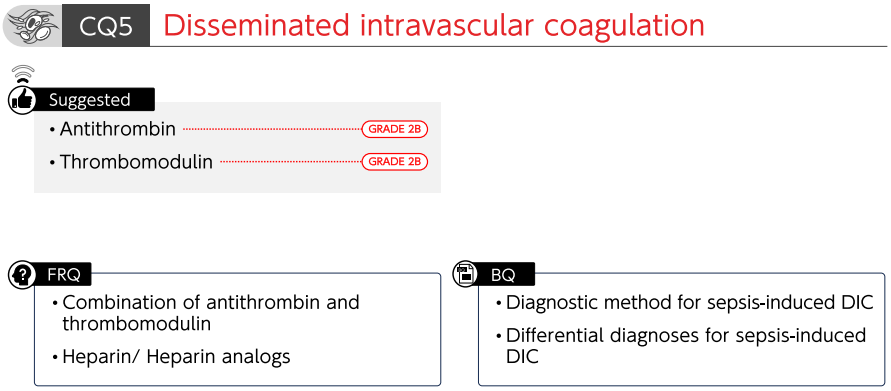

FIGURE 5 Summary of recommendations (CQ5 Disseminated intravascular coagulation). BQ, background question; CQ, clinical question; DIC; disseminated intravascular coagulation; FRQ, future research question.

criteria are used to diagnose progressed DIC and predict mortality (*Provision of information for background question*).

Rationale

The first diagnostic criteria for DIC, the Japanese Ministry of Health and Welfare DIC diagnostic criteria, were established in 1979, followed by the ISTH overt DIC, JAAM DIC, and SIC. The JAAM DIC diagnostic criteria, which are widely used in clinical practice in Japan, included the SIRS score and considered the rate of decrease in platelet count over time in addition to the platelet count at a certain cut-off as diagnostic items, aiming to sensitively detect inflammation-associated coagulation abnormalities.[359] The SIC diagnostic criteria included the SOFA score as a diagnostic item, in addition to the routine test of prothrombin time (PT) and platelet count, which is consistent with the change in sepsis diagnostic criteria from the SIRS score to the SOFA score.[360] The overt DIC diagnostic criteria, which are commonly used internationally, are stricter than the JAAM-DIC or SIC diagnostic criteria, and they are used to avoid overdiagnosis and identify severe DIC cases.[361]

These diagnostic criteria can be used according to the purpose, as there is no gold standard for DIC diagnosis, and it is difficult to assess which criteria are superior to others. The JAAM-DIC and SIC diagnostic criteria are used to diagnose early DIC and determine treatment initiation, whereas the ISTH overt DIC diagnostic criteria are used to diagnose progressed DIC and predict mortality.

CQ5-2: What are the differential diagnoses for patients with suspected sepsis-induced DIC?

Answer: DIC-like clinical conditions include TMA and HIT, which require differential diagnosis (*Provision of information for background question*).

Rationale

In ICUs, 9–19% of thrombocytopenia cases are caused by DIC,[362] and sepsis-induced DIC accounts for the majority of these cases. However, some clinical conditions that require different treatment strategy also cause blood test abnormalities similar to those of DIC. Although anticoagulat therapy is considered effective for DIC, it is not only ineffective for such clinical conditions, but may also be harmful. Therefore, it is important to differentiate between sepsis-induced DIC and its similar clinical conditions. In patients with TMA prompt specific treatments can improve mortality or prevent serious sequelae. Thrombotic microangiopathy has three main symptoms as follows; microangiopathic hemolytic anemia, consumptive thrombocytopenia, and organ damage due to microvascular platelet thrombosis. Prolonged PT and elevated fibrin degradation product (FDP) observed in DIC are usually absent or mild.[363]

Sepsis-induced DIC should be diagnosed promptly. However, even if a patient is diagnosed with DIC, the actual diagnosis may be TMA instead of DIC or TMA concurrently with DIC. If the patient exhibits poor response to DIC treatment or atypical clinical signs, clinicians should consider the possibility of TMA, and prompt diagnosis and conversion to specific treatment (such as plasma exchange and molecular target drug) are required.

Other diseases that need to be differentiated from sepsis-induced DIC except TMA include HIT, hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome, and severe hepatic dysfunction.[364–366] For any of these diseases, thrombocytopenia can be the trigger for diagnosis.

CQ5-3: Is antithrombin administered for sepsis-induced DIC?

Answer: We suggest the administration of antithrombin for sepsis-induced DIC (GRADE 2B).

Rationale

Antithrombin has anticoagulant effects, mainly by inhibiting thrombin and activated factor X. Additionally, it has an anti-inflammatory effect that may help control sepsis-induced DIC.[367] Previous meta-analyses have conflicting results regarding its contribution to improving the prognosis of sepsis-induced DIC, and no clear evidence has been

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established.[368,369] The J-SSCG2020 suggested the administration of antithrombin (GRADE 2C).[8,9]

We conducted a meta-analysis of five RCTs using a decrease in mortality and recovery from DIC as desirable effects.[370–374] Concerning the desirable effects of antithrombin, the analysis of the five RCTs[370–374] showed that mortality yielded a RD of 147 fewer per 1000 (95% CI: 214 fewer to 67 fewer), and analysis of three RCTs[370,371,374] showed that recovery from DIC yielded an RD of 448 more per 1000 (95% CI: 161 more to 999 more). Concerning the undesirable effect of antithrombin, analysis of the three RCTs[370,373,374] showed that bleeding complications yielded an RD of 8 more per 1000 (95% CI: 24 fewer to 89 more). Considering the relative value of each outcome, the desirable effects were large, and the undesirable effects were trivial. Thus, we concluded that the balance of effects was better for the intervention (Data S3).

Future studies would clarify issues, such as the optimal dosage, target activity levels, and criteria for starting and discontinuing administration. In clinical practice, individual decision must be made, depending on the general conditions of patients.

CQ5-4: Is recombinant thrombomodulin administered for sepsis-induced DIC?

Answer: We suggest the administration of recombinant thrombomodulin for sepsis-induced DIC (GRADE 2B).

Rationale

Recombinant thrombomodulin has an anticoagulant effect by binding to thrombin and activating protein C. In addition, it exerts an anti-inflammatory effect through its lectin-like domain.[375] However, there has been no sufficient evidence for recombinant thrombomodulin in patients with sepsis, and no definitive conclusion has been reached on its efficacy.[376–378] Therefore, we evaluated recombinant thrombomodulin for sepsis-induced DIC.

We conducted a meta-analysis of four RCTs,[379–382] using a decrease in mortality as a desirable effect. The results showed that mortality yielded an RD of 39 fewer per 1000 (95% CI: 75 fewer to 3 more). Additionally, a meta-analysis of three RCTs[380–382] showed that recovery from DIC yielded an RD of 120 more per 1000 (95% CI: 4 more to 274 more), also considered a desirable effect.

For adverse effects, another meta-analysis of four RCTs[379–382] showed that bleeding complications yielded an RD of 12 more per 1000 (95% CI: 6 fewer to 41 more). Considering the relative value of each outcome, we found that the beneficial effects were substantial, while the adverse effects were minimal. Thus, we concluded that the balance of effects was probably better for the intervention (Data S3).

The frequency and risk of hemorrhagic complications in sepsis-induced DIC vary, depending on the pathophysiology and presence or absence of invasive treatment. Thus, clinicians should exercise caution regarding bleeding complications when administering recombinant thrombomodulin.

FRQ5-1: Are antithrombin and thrombomodulin concomitantly administered for sepsis-induced DIC?

Rationale

The J-SSCG 2020 recommended the administration of antithrombin or recombinant thrombomodulin for sepsis-induced DIC.[8,9] In Japan, some facilities use combination therapy with antithrombin and recombinant thrombomodulin, but there is currently no consistent opinion on its effectiveness. Thus, the present guidelines covered the concomitant administration of antithrombin and recombinant thrombomodulin for sepsis-induced DIC as an FRQ. We conducted a meta-analysis of seven observational studies[383–390] and examined the usefulness of the combination therapy for sepsis-induced DIC using a random-effects model. As a result of the combination therapy, there was a decreasing tendency in mortality rate (odds ratio: 0.89, 95% CI; 0.74–1.07, heterogeneity: 72%), although there was no significant difference. Additionally, the incidence of hemorrhagic complications in the combination therapy was comparable to that in monotherapy. This meta-analysis has several limitations, including that all of the studies were conducted in Japan, that they were observational studies rather than RCTs, and that there was a statistically high heterogeneity. Therefore, we currently present the CQ as an FRQ without providing any recommendations.

FRQ5-2: Is heparin or heparin analogs administered for sepsis-induced DIC?

Rationale

The J-SSCG2020 suggested against the administration of heparin or heparin analogs for sepsis-induced DIC.[8,9] However, heparin administration in the pathophysiology of sepsis is attracting renewed attention based on the usefulness of heparin for coagulation abnormalities in patients with COVID-19, as well as several reports suggested the effect of heparin in improving the prognosis of sepsis and sepsis-induced DIC.[391–393] Therefore, in order to reconsider the possibility of heparin and heparin analogs, the present guidelines mentioned them as an FRQ.

A systematic review by Fu et al. has suggested that the administration of heparin for patients with sepsis may improve prognosis.[394] Additionally, a study using the US Medical Information Mart for Intensive Care-IV database for SIC reported that the early administration of heparin improved ICU mortality rate.[395] Heparin may be useful, depending on the timing of administration and selected target. A systematic review by Li et al. reported that the

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administration of low-molecular-weight heparin for patients with sepsis may improve prognosis and reduce hemorrhagic risk.[396] However, we set the CQ as an FRQ without providing any recommendations because we found that there was insufficient evidence to provide a recommendation from the perspective of the risk of bias. Large-scale RCTs and high-quality observational studies are needed to clarify the effectiveness of heparin and heparin analogs for sepsis.

CQ6 Adjuvant therapy

CQ6-1: Is IVIG administered for sepsis?

Answer: We suggest against the administration of IVIG for sepsis (GRADE 2C).

Rationale

IVIG includes specific antibodies against various bacteria, toxins, and viruses. Immunoglobulin neutralizes pathogenic microorganisms and toxins, promote phagocytosis and bacteriolysis through complement activation, has opsonic, antibody-dependent cellular cytotoxic, non-specific anti-inflammatory effects, and suppresses inflammatory cytokine production. Patients with sepsis have decreased serum immunoglobulin G (IgG) levels from the early stage of onset due to decreased production, capillary leakage, and wasting consumption. The incidence of shock and mortality rate increase significantly if serum IgG levels are severely decreased.[397,398] Based on the background of the aforementioned studies, the administration of IVIG along with appropriate systemic management and early administration of antimicrobials may improve prognosis.

We performed a meta-analysis of nine published RCT.[399–407] As a result of IVIG administration, the adverse events yielded an RD of 1 fewer per 1000 (95%CI: 23 fewer to 46 more; two RCTs, 724 patients).[400,401] In contrast, the short-term mortality yielded an RD of 14 more per 1000 (95% CI: 51 fewer to 88 more; three RCTs, 745 patients).[399–401] Considering these results, we concluded that the balance of effects was probably better for the comparator (Data S3).

The use of IVIG as a standard treatment is undesirable. However, we do not exclude the indications in special pathophysiological conditions, such as STSS.[408,409] This point has been summarized in FRQ6-1.

CQ6-2: Is high-dose vitamin C therapy used for sepsis?

Answer: We suggest against the use of high-dose vitamin C therapy for sepsis (GRADE 2B).

Rationale

Vitamin C, a water-soluble vitamin, cannot be synthesized within the body. It has been reported in recent years that high-dose administration of vitamin C may improve survival rate in patients with sepsis.[410] Many RCTs have been conducted,[411–428] and there is a concern that administration of high-dose vitamin C may cause kidney injury.

We conducted a meta-analysis of 18 published RCTs.[411–428] With regards to mortality, long-term mortality (≥60 days) was adopted as an outcome, as we decided to adopt the outcome with the highest certainty of evidence. As a result of high-dose vitamin C administration, the long-term mortality yielded an RD of 23 more per 1000 (95% CI: 15 fewer to 69 more; six RCTs, 2148 patients),[411–416] and AKI yielded an RD of 26 more per 1000 (95% CI: 34 fewer to 104 more; six RCTs, 1846 patients).[412,413,416–419] The balance of effects was probably better for the comparator (Data S3).

This recommendation concerns the administration of high-dose vitamin C to patients with sepsis, and it does not discourage the administration of standard-dose vitamin C as a nutritional therapy.

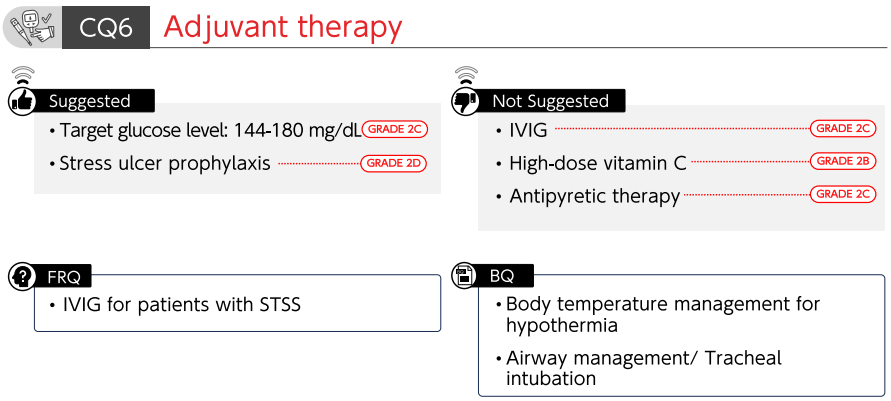
CQ6 Adjuvant therapy
Suggested
• Target glucose level: 144-180 mg/dL GRADE 2C
• Stress ulcer prophylaxis GRADE 2D
Not Suggested
• IVIG GRADE 2C
• High-dose vitamin C GRADE 2B
• Antipyretic therapy GRADE 2C
FRQ
• IVIG for patients with STSS
BQ
• Body temperature management for hypothermia
• Airway management/ Tracheal intubation

FIGURE 6 Summary of recommendations (CQ6 Adjuvant therapy). BQ, background question; CQ, clinical question; FRQ, future research question; IVIG, intravenous immunoglobulin; STSS, streptococcal toxic shock syndrome.

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CQ6-3: What is the target blood glucose level for sepsis?

Answer: We suggest 144–180 mg/dL as a target blood glucose level for sepsis (GRADE 2C).

Rationale

It has been recommended that the glucose control in an ICU should avoid both low (< 110 mg/dL)[429] and high (≥ 180 mg/dL) ranges. However, there is a question as to whether there is a difference in the incidence of hypoglycemia between blood glucose levels near 110 mg/dL and 180 mg/dL. To clarify this question, we divided the range of blood glucose levels (110–180 mg/dL) into two based on the NICE-SUGAR study[430]: 110–144 and 144–180 mg/dL. We then conducted a network meta-analysis (NMA) using the four range of blood glucose levels as follows: <110 mg/dL, 110–144, 144–180, and ≥180 mg/dL.

An NMA was performed using 36 RCTs.[8,9,429–464] As a result, the balance of effects among the groups was summarized as follows. A range of <110 mg/dL was inferior to all the other ranges. Second, a range of 144–180 mg/dL was superior to 110–144, and ≥180 mg/dL was not superior to 110–144 mg/dL. Finally, values ≥180 mg/dL was not superior to 144–180 mg/dL. Therefore, we observed that 144–180 mg/dL was the most optimal target level (Data S3).

To prevent insulin-induced hypoglycemia, it is important to measure blood glucose at appropriate intervals during continuous administration of insulin. However, we did not examine appropriate intervals of blood glucose measurement. The European Society for Clinical Nutrition and Metabolism guideline recommended measuring blood glucose at least every 4 h for 48 h after ICU admission as good practice points, and stated that more frequent measurements may be needed, depending on patients' conditions.[465]

Methods for measuring blood glucose levels in acute-phase conditions include measurements using blood biochemical testing in a laboratory, blood gas analyzer, or a simple blood glucose meter with arterial/venous and capillary blood. Measurement using glucometer with capillary blood can result in significant errors and have a risk of overlooking hypoglycemia.[8,9]

CQ6-4: Is antipyretic therapy provided to febrile patients with sepsis?

Answer: We suggest against antipyretic therapy for febrile patients with sepsis (GRADE 2C).

Rationale

Patients with sepsis frequently develop fever, which causes patient discomfort, increased oxygen demand, and central nervous system disorders. On the other hand, fever serves as a defense reaction that activates the immune system and is associated with the promotion of the elimination of pathogenic microorganisms. Antipyretic therapy is frequently administered to reduce discomfort and oxygen demand and prevent central nervous system disorders. However, because it may also suppress defense reaction, the balance of its benefits and harms needs to be clarified.

We conducted a meta-analysis of seven published RCTs that examined antipyretic therapy comprising acetaminophen, extracorporeal cooling, or a combination of both, compared with a non-intervention group.[466–472] Six RCTs examined drug therapy[466,467,469–472] (one of the RCTs examined the concomitant use of antipyretics with body-surface cooling[467]), while one RCT examined intervention using body-surface cooling.[468] As a result of the antipyretic therapy, 28- or 30-day mortality yielded an RD of 43 more per 1000 (95% CI: 48 fewer to 174 more; four RCTs, 1236 patients).[466–469] Additionally, all serious adverse events yielded an RD of 1 more per 1000 (39 fewer to 74 more; four RCTs, 1312 patients),[466,469–471] and infectious complications yielded an RD of 28 fewer per 1000 (70 fewer to 54 more; three RCTs, 510 patients).[466,467,472] The effects of antipyretic therapy were limited. Thus, we concluded that the balance of effects was probably better for the comparator (Data S3). However, this suggestion may not be applied in remarkable hyperthermia or in cases where alleviating fever-associated symptoms is prioritized.

CQ6-5: Is stress ulcer prophylaxis performed for patients with sepsis to prevent gastrointestinal hemorrhage?

Answer: We suggest performing stress ulcer prophylaxis for patients with sepsis to prevent gastrointestinal bleeding (GRADE 2D).

Rationale

Since stress ulcer may cause gastrointestinal bleeding in intensive care patients, pharmacological ulcer prophylaxis is indicated. However, there are concerns about the side effects of antacids, such as pneumonia and *Clostridioides difficile* infection. Therefore, it is necessary to clarify the balance of benefits and harms of the prophylactic use of antacids.

We conducted a meta-analysis of 32 published RCTs and one additional outcome report evaluating the effects of stress ulcer prophylaxis in non-specific intensive care patients.[473–505] The following five outcomes were assessed: gastrointestinal bleeding (30 RCTs, 6866 patients),[473–502] mortality (14 RCTs, 5065 patients),[473,475,477,480,482,487,488,490,491,496,498,500,503,504] pneumonia (15 RCTs, 5146 patients),[473,475,477,479,485,487,488,490–494,500,503,505] serious adverse events (seven RCTs, 4143 patients)[477,487,488,495,497,500,503] and *Clostridioides* infection (three RCTs, 3607 patients).[480,500,503] Regarding desirable effects, gastrointestinal bleeding yielded an RD of 66 fewer per 1000 (95% CI: 84 fewer to 43 fewer), and *Clostridioides* infection yielded an RD of 4 fewer per 1000 (9 fewer to 5 more). In contrast, mortality rate yielded an RD of 10 more

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per 1000 (13 fewer to 36 more), and pneumonia yielded an RD of 8 more per 1000 (12 fewer to 29 more). Serious adverse events also yielded an RD of 5 more per 1000 (6 fewer to 20 more). Considering the relative value of each outcome, we concluded that the balance of effects was probably better for the intervention (Data S3). It should be noted that this recommendation was drawn from data of patients receiving intensive care, but not specific for patients with sepsis.

CQ6-6: How is the body temperature managed in septic patients with hypothermia?

Answer: Rewarming therapy might be rational when hypothermia-associated circulatory disorders or coagulation abnormalities are observed in septic patients with hypothermia (core body temperature of <35°C). However, caution should be taken as rewarming therapy may cause peripheral vasodilation, resulting in adverse events, such as hypotension (*Provision of information for background question*).

Rationale

Hypothermia is one of the body temperature abnormalities that occur in patients with sepsis. Septic patients with hypothermia have poor prognosis, and hypothermia affects the defense mechanism against microbial infection and causes complications, such as decreased cardiac function, arrhythmia, electrolyte abnormalities, and coagulopathy.

Hypothermia is independently associated with poor prognosis in patients with sepsis.[506] A multicenter observational study in Japan reported that 11.1% of patients with sepsis had hypothermia of <36°C at the time of ICU admission.[507] Compared to patients with body temperature > 38°C at the time of ICU admission, unadjusted odds ratio of hospital mortality for patients with hypothermia (< 36°C) was 1.76 (95% CI: 1.13–2.73), indicating a poor prognosis for septic patients with hypothermia.[507]

Hypothermia (core body temperature of <35°C) leads to decreased immune function due to dysregulation of inflammatory cytokines, such as interleukin 6 and tumor necrosis factor-α, and lymphopenia.[508] Hypothermia causes decreased cardiac function, arrhythmia, cold diuresis, electrolyte abnormalities, and coagulation abnormalities, and severe hypothermia develops unstable hemodynamics and hemorrhagic tendency.[509–511] Based on these serious complications, rewarming might be rational in septic patients with hypothermia.[512] A questionnaire survey described that 96% of respondents reported that there was no protocol for the management of hypothermic sepsis, although 62% of the respondents actively rewarmed patients with hypothermic sepsis.[513] When providing rewarming therapy, attention should be paid to the occurrence of adverse events, such as hypotension due to peripheral vasodilatation, altered the balance between oxygen demand and supply, and electrolyte abnormalities.[514,515]

No RCTs have been conducted on rewarming therapy for septic patients with hypothermia. The balance of benefits and harms of rewarming therapy may differ for each patient. Therefore, physicians need to assess whether or not rewarming therapy is necessary, considering the severity of hypothermia and rewarming-associated complications.

CQ6-7: How is tracheal intubation performed for patients with sepsis?

Answer: Pathophysiological conditions for which tracheal intubation is indicated in patients with sepsis include shock and imbalance between oxygen demand and supply, in addition to airway obstruction and hypoxemia. Because sedatives and analgesics used during tracheal intubation may cause hemodynamic fluctuations, it is important to perform appropriate hemodynamic management, such as preparation of vasopressors (*Provision of information for background question*).

Rationale

Tracheal intubation and mechanical ventilation are required in 40–85% of patients with septic shock for a variety of reasons.[516] A previous review described that complications occurred in 45% of critically ill patients receiving tracheal intubation outside an operating room.[517]

Indications for tracheal intubation is divided into problems in airway and gas exchange. Furthermore, insufficient oxygen supply relative to its demand, such as in patients with shock or circulatory failure, is also indicated because it has been suggested that oxygen supply to vital organs can be maintained by mechanical ventilation in patients with shock.[518]

Physiological abnormalities, such as metabolic acidosis, are often present in sepsis. In these patinets, positive pressure ventilation itself can trigger circulatory collapse.[517,519] Therefore, physiological abnormalities should also be considered in addition to anatomical factors during tracheal intubation for patients with sepsis.[519] Evaluation of the airway, adequate preoxygenation before tracheal intubation, and preparation of drugs and tracheal intubation devices are important in order to reduce complications associated with tracheal intubation.[517]

Requiements of analgesics and sedatives during tracheal intubation is reduced in critically ill patients.[520] Clinicians should pay attention to hemodynamic and respiratory failure immediately after tracheal intubation.[520] A recent review shows that fluid loading and early introduction of vasopressors together may decrease the occurrence of intubation-related hemodynamic complications.[521]

First-attempt failure was reported to be a contributing factor to periprocedural complications and death in tracheal intubation.[521] Methods for improving the successful intubation rates and reducing the incidence of difficult intubations include the use of stylet[522] and video laryngoscopes. To obtain the cooperation of physicians who are skilled in tracheal intubation is also important in order to safely and reliably perform tracheal intubation in patients with sepsis.

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FRQ6-1: Is IVIG administered for patients with STSS?

Rationale

Streptococcal toxic shock syndrome or severe invasive streptococcal infection can progress rapidly to hypotension and multiple organ failure. It has a high mortality rate of approximately 40%,[523,524] with the majority of deaths occurring within a few days after onset.[525] However, STSS is caused by the exotoxin produced by group A *Streptococcus*. IVIG, which has the effect of neutralizing toxins and suppressing cytokine production, may improve the clinical conditions of STSS.[526]

A systematic review analyzing one published RCT[399] and several observational studies showed that the administration of IVIG was associated with improved prognosis.[408,409] In the J-SSCG 2020, we performed an analysis limited to adult patients with STSS and obtained similar results.[8,9] However, there are some negative opinions about the administration of IVIG for the low certainty of evidence in the aforementioned systematic review and different titer of neutralizing antibodies for each IVIG formulation.[524] Additionally, there are no clear administration protocols regarding IVIG dosage. In one RCT, 1 g/kg was administered on the first day of treatment, followed by 0.5 g/kg on the second and third days.[399] Recently, the administration of 25 g IVIG per dose has been reported to be effective in neutralizing toxins, and a protocol of administering 0.5 g/kg on the first day of treatment, followed by 25 g on the second and third days, has been proposed.[527]

CQ7 Post-intensive care syndrome

CQ7-1: Is early rehabilitation implemented to prevent PICS?

Answer: We suggest conducting early rehabilitation to prevent PICS (GRADE 2D).

Rationale

Early rehabilitation can prevent PICS in patients admitted into an ICU. However, the benefit and harm of early rehabilitation for patients with sepsis have not been established. Additionally, there is no consensus regarding its definition and details for intervention. The J-SSCG 2020 suggested early rehabilitation for the prevention of PICS in patients with sepsis and those that are critically ill.[8,9] Based on subsequent findings, the present CQ examined the efficacy of early rehabilitation in preventing PICS.

We conducted a meta-analysis of five RCTs evaluating the effect of early rehabilitation.[528–532] The SMD in muscle strength after discharge was 0.16 higher (95% CI: 0.08 lower to 0.40 higher), and the MD in cognitive function after discharge was 0.6 higher (95% CI: 0.25 lower to 1.45 higher). Additionally, the MD in mental function after discharge was 0.3 high (95% CI: 4.92 lower to 5.52 higher), and the SMD in activity of daily living after discharge was 0.57 high (95% CI: 0.1 higher to 1.05 higher). Any adverse events yielded an RD of 7 fewer per 1000 (95% CI: 58 fewer to 124 more), but short-term mortality yielded an RD of 11 more per 1000 (95%CI: 36 fewer to 77 more), which was considered an undesirable effect. Considering the importance of short-term mortality, we concluded that the balance of effects was probably better for the intervention (Data S3).

CQ 7-2: Is neuromuscular electrical stimulation used to prevent ICU-AW?

Answer: We suggest using neuromuscular electrical stimulation to prevent ICU-AW (GRADE 2C).

Rationale

Sepsis itself and the use of vasopressors are risk factors for developing ICU-acquired weakness (ICU-AW). Neuromuscular electrical stimulation is expected to be effective in preventing muscle weakness in critically ill patients. However, it is difficult to achieve effective muscle contraction through neuromuscular electrical stimulation in sepsis patients, patients

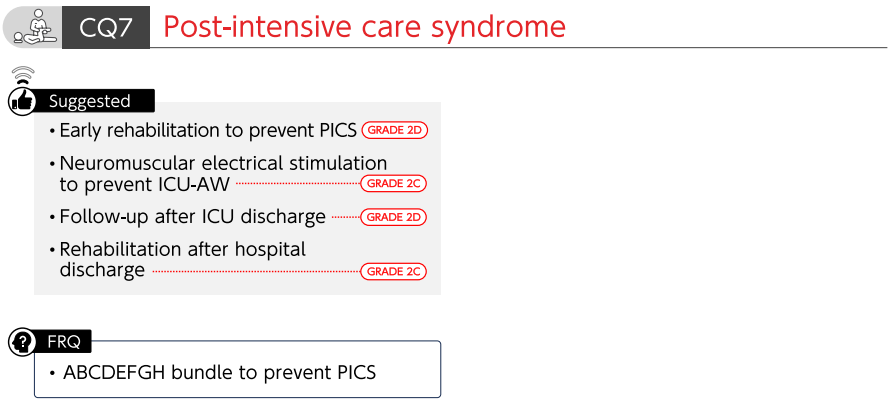
CQ7
Post-intensive care syndrome
Suggested
• Early rehabilitation to prevent PICS GRADE 2D
• Neuromuscular electrical stimulation to prevent ICU-AW GRADE 2C
• Follow-up after ICU discharge GRADE 2D
• Rehabilitation after hospital discharge GRADE 2C
FRQ
• ABCDEFGH bundle to prevent PICS

FIGURE 7 Summary of recommendations (CQ7 Post-intensive care syndrome). CQ, clinical question; FRQ, future research question; ICU-AW, intensive care unit- acquired weakness; PICS, post-intensive care syndrome.

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requiring vasopressor drugs, and patients with edema,[533] and its efficacy remains unclear. J-SSCG 2020 suggested against performing neuromuscular electrical stimulation to prevent ICU-AW in sepsis patients and critically ill patients.[8,9] The present CQ examined the efficacy of neuromuscular electrical stimulation in preventing the development of ICU-AW and its effect on quality of life (QOL).

We conducted a meta-analysis of 15 RCTs evaluating the effect of neuromuscular electrical stimulation.[534–548] The incidence rate of ICU-AW at ICU discharge yielded an RD of 218 fewer per 1000 (95% CI: 285 fewer to 117 fewer), and the MD in health-related QOL after ICU discharge was 0.2 higher (95% CI: 0.03 lower to 0.43 higher). On the other hand, short-term mortality yielded an RD of 18 more per 1000 (95% CI: 33 fewer to 79 more), and any adverse events yielded an RD of 10 more per 1000 (95% CI: 20 fewer to 40 more). Considering the relative value of each outcome, we concluded that the balance of effects was probably better for the intervention (Data S3).

CQ7-3: Is follow-up after ICU discharge be implemented to improve physical, cognitive, and mental functions?

Answer: We suggest conducting follow-up after ICU discharge to improve physical, cognitive, and mental functions (GRADE 2D).

Rationale

Many survivors who have been admitted to the ICU develop PICS, and they experience difficulties in returning to daily life and work due to physical, cognitive, and mental dysfunctions developed during ICU stay and after ICU discharge. Follow-up rounds for PICS after ICU discharge (PICS rounds) and follow-up outpatient visits after hospital discharge are aimed at improving physical, cognitive, and mental functions. However, evaluation of the benefit and harm of follow-up for patients with sepsis after ICU discharge has not been established.

We conducted a meta-analysis of three RCTs evaluating the effect of follow-up after ICU discharge.[549–551] The MD in physical function after hospital discharge was 15 lower (95% CI: 25.41 lower to 4.59 lower), and the SMD in mental function (depression) after hospital discharge was 0 lower (95% CI: 0.19 lower to 0.19 higher). There were no studies reporting any adverse events. On the other hand, the MD in cognitive function after hospital discharge was 0.3 lower (95% CI: 1.35 lower to 0.75 higher), and the SMD in mental function (post-traumatic stress disorder, PTSD) after hospital discharge was 0.1 higher (95%CI: 0.42 lower to 0.62 higher), which were considered undesirable effects. Considering the results of cognitive and mental functions after discharge, we concluded that the balance of effects was probably better for the intervention (Data S3). Follow-up methods after ICU discharge depending on the circumstances of each facility, as well as the establishment of selection criteria for target patients, are considered.

CQ7-4: Is rehabilitation after hospital discharge implemented to improve physical, cognitive, and mental functions?

Answer: We suggest performing rehabilitation after hospital discharge to improve physical, cognitive, and mental functions (GRADE 2C).

Rationale

Many survivors who have been admitted to the ICU develop PICS, and they experience decreased QOL and poor long-term prognosis due to physical, cognitive, and mental dysfunctions developed during hospitalization and after hospital discharge. Enhanced rehabilitation after hospital discharge aims at improving physical, cognitive, and mental functions. However, benefit and harm of post-hospital discharge rehabilitation for sepsis patients have not been established.

We conducted a meta-analysis of nine RCTs evaluating the effect of performing rehabilitation after ICU discharge.[552–560] The SMD in physical function after hospital discharge was 0.17 higher (95% CI: 0.17 lower to 0.52 higher), and the MD in cognitive function after hospital discharge was 3.5 higher (95% CI: 1.56 higher to 5.44 higher). Also, the MD in mental impairment (depression) after hospital discharge was 0.24 lower (95% CI: 3.53 lower to 3.05 higher). On the other hand, any adverse events yielded an RD of 29 more per 1000 (95% CI: 2 more to 107 more). Based on these results, we concluded that the balance of effects was probably better for the intervention (Data S3).

Each facility needs to establish the selection criteria for target patients for post-hospital discharge intensive rehabilitation depending on the circumstances. Upon implementation, the timing, duration, intensity, duration, and frequency are stipulated by healthcare providers, depending on the circumstances of the patients.

FRQ7-1: Is the ABCDEFGH bundle implemented to prevent PICS?

Rationale

It is often difficult to achieve a complete cure of PICS in its natural course, and thus, its prevention and early intervention are crucial. Experts proposed the ABCDEFGH bundle for the prevention of PICS (Table 5). The ABCDEFGH bundle is a concept in which "FGH" to reduce PICS or PICS-F has been added to the ABCDE bundle proposed in 2010 to comprehensively improve the management of mechanically ventilated patients.[561–563] Large-scale multicenter observational studies of critically ill adult patients have reported that a high rate of adherence to the ABCDEF bundle is associated with decreases in hospital mortality and delirium incidence.[564,565] At present, no clinical studies have evaluated the effectiveness of PICS/PICS-F prevention in the

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TABLE 5 ABCDEFGH bundle.

A: Assess, prevent, and manage pain	To understand pain and use tools for its assessment, treatment, and prevention
B: Both SAT and SBT	To use spontaneous awakening trial and spontaneous breathing trial in combination
C: Choice of analgesia and sedation	To understand the importance of depth of sedation and select appropriate drugs
D: Delirium: Assess, prevent, and manage	To understand risk factors for delirium and use tools for their assessment, treatment, and prevention
E: Early mobility and exercise	Early mobilization and rehabilitation in the ICU do not just change the body position of patients
F: Family engagement and empowerment, Follow-up referrals, Functional reconciliation	Patients' recovery can be facilitated by engaging family members in their care To make follow-up referrals and functional reconciliation
G: Good handoff communication	To establish good handoff communication
H: Hand the patients and family written information about PICS or PICS-F	To provide patients and their families with written information regarding PICS and PICS-F

Note: Created from references.[561–563,566]

Abbreviations: ICU, intensive care unit; PICS, post-intensive care syndrome; PICS-F, post-intensive care syndrome family; SAT, spontaneous awakening trial; SBT, spontaneous breathing trial.

entire ABCDEFGH bundle as outcomes. Studies on the effectiveness of the ABCDEFGH bundle, which incorporates comprehensive prevention of PICS including post-ICU discharge, are needed.

CQ8 Patient and family care

CQ 8-1: Is written information provided to the families of critically ill patients?

Answer: We suggest providing information related to intensive care to the families of critically ill patients in written or other forms (GRADE 2C).

Rationale

Many families of critically ill patients treated in an ICU have trouble in understanding their patients' conditions due to unfamiliar medical information and inadequate communication with healthcare providers. Several studies have suggested that written information provision to the families of critically ill patients, in addition to verbal explanations by healthcare providers, is associated with a reduced psychological symptom of the families and improvement of their satisfaction and understanding.[567,568] However, its effects have not yet been validated.

We conducted a meta-analysis of six RCTs.[567–572] As a result of written information provision related to intensive care to families of critically ill patients, the SMD in families' anxiety was 0.27 lower (95% CI: 0.68 lower to 1.13 higher), the SMD in families' depression was 0.23 lower (95% CI: 0.54 lower to 0.08 higher), and the MD in families' stress disorder was 9.39 lower (95% CI: 13.47 lower to 5.3 lower). The MD in families' satisfaction (a lower value indicates a higher satisfaction) was 1.26 lower (95% CI: 2.35 lower to 0.17 lower). The families' understanding yielded a RD of 295 more per 1000 (95% CI: 142 more to 479 more). There were no reports of adverse events resulting from the information provision. Based on these results, we concluded that the balance of effects was better for the intervention (Data S3).

In the RCTs included in this meta-analysis, patients' severity and the methods of information provision varied. Therefore, it is necessary to confirm the patients' and their families' values and consider the compliance of families and the methods of information provision before implementing the intervention.

CQ 8-2: What is the relaxation of visitation restrictions for families of critically ill patients?

Answer: Relaxation of visitation restrictions for families of critically ill patients include unrestricted visiting hours or numbers of visitors and online visitation. There is an opinion that it may be effective in preventing PICS-F. Its necessity should be considered depending on the situation at one's own facility and individual cases (*Provision of information for background question*).

Rationale

Visitation restriction is necessary in preventing the spread of infection, ensuring the rest and safety of patients, improving the work efficiency of healthcare providers, and protecting privacy.[573,574] In contrast, visitation restrictions may make it difficult for family members to obtain information about patients and pose a hindrance on patient and family members-centered care, resulting in increased risk of developing PICS-F. To solve this problem, relaxation of visitation restrictions has been proposed. Large-scale RCTs of adult ICU patients have shown that relaxation of visitation restrictions based on the provision of appropriate information can be implemented without increasing the incidence of infection or burnout rate of healthcare providers, and that it might reduce the anxiety of family members and increase their satisfaction level.[575,576] A recent meta-analysis showed that relaxation of visitation restrictions was associated with decreased incidence of delirium in patients and shorter length of ICU stay without an increasing risk of infection.[577] A large-scale retrospective observational study reported that the incidence of mental disorders in patients during the

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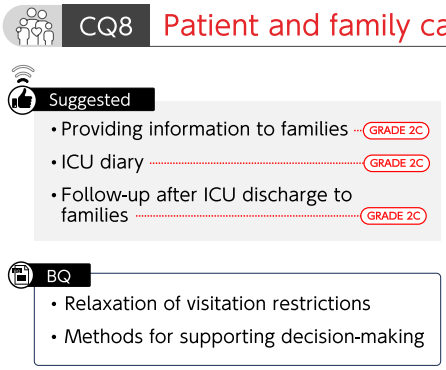
CQ8 Patient and family care
Suggested
• Providing information to families GRADE 2C
• ICU diary GRADE 2C
• Follow-up after ICU discharge to families GRADE 2C
BQ
• Relaxation of visitation restrictions
• Methods for supporting decision-making

FIGURE 8 Summary of recommendations (CQ8 Patient and family care). BQ, background question; CQ, clinical question; ICU, intensive care unit.

first year after hospital discharge decreased by 21% with in-person family visits.[578]

Since the COVID-19 pandemic, strict restrictions, including prohibitions for visiting, have been implemented. Relaxation of visitation restrictions is fraught with more complex issues than ever. Assessment regarding whether or not to allow visitation is carefully made from various perspectives, such as the risk of epidemiology of infectious diseases, burden on healthcare providers, and protection of patient privacy. It is important to decide how to not to restrict visitation based on the social situation, policies and circumstances of their own facility, and patients' conditions.

CQ 8-3: What are the methods for supporting decision-making that respect the value systems and ways of thinking in a patient?

Answer: There are methods of supporting decision-making that respect the values systems and ways of thinking of a patient through repeated discussions at multidisciplinary conferences involving patients and their families. One of the methods proposed is careful estimation through surrogate decision makers (e.g., family members) when the intentions of a patients are unclear. While respecting the intentions of patients, appropriate medical information is provided to patients and their families (*Provision of information for background question*).

Rationale

Decision-making support is becoming increasingly important with the increasing complexity of medical care and diversification of values, views, and lifestyles of patients. Emphasis has been placed on respecting patients' right to know, right of self-determination, and principles of autonomy, and shared decision making and advance care planning (ACP) have been proposed. Shared decision making is a concept in which patients, their families, and acquaintances and friends whom the patient trusts in making decisions proceed with decision-making together with healthcare providers. Decisions are made through a continuous two-way process; healthcare providers present accurate information that serves as evidence for the patient's condition and treatment options/methods, while the patient and patient's family provide information about the patient's own values and wishes. They organize medical facts, have discussions at multidisciplinary conferences based on decisions made by the patient him/herself, and decide on the best policy for the patient.[579] ACP is important in this decision-making process; in order to provide information, including the values/wishes of the patient and medical care that the patient desires, it is necessary for a patient and his/her family to have an advance discussion in anticipation of emergencies, that is, ACP. When the intentions of a patient cannot be confirmed, surrogate intention-estimating individuals, such as family members, are carefully identified, and the best policy for the patient is taken while respecting the estimated intentions of the patient based on ACP. Shared decision making using ACP may reduce stress, depression, and anxiety in families after bereavement.[567,580] These methods are not perfect even when a decision is made, and they are repeated over time, depending on changes in clinical course including patient's physical and mental conditions, and prognostication. The contents of each discussion during this process are summarized and recorded in medical records.[579]

CQ 8-4: Is an ICU diary kept for critically ill patients?

Answer: We suggest keeping an ICU diary for critically ill patients (GRADE 2C).

Rationale

Critically ill patients treated in the ICU often have consciousness disorders or are under sedation due to their severe conditions. In the ICU, critically ill patients develop memory loss or delusional memories, in which events that did not actually occur are recalled as vivid memories. An ICU diary is an intervention that assists in the correct organization and reconstruction of memories by having healthcare providers, family members, and other individuals write a diary about the patient's daily situations in the ICU and hand over the diary to the patient after achieving recovery. Multiple studies have shown that ICU diary is associated with reductions in stress disorders, anxiety, and depression symptoms in critically ill patients and their families. However, its effectiveness and adverse events have not yet been validated.

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We conducted a meta-analysis of six RCTs.[581–586] As a result of keeping an ICU diary for critically ill patients, the SMD in the level of stress disorder in patients was 0.13 lower (95% CI: 0.32 lower to 0.06 higher), and the MD in the level of anxiety was 1.15 lower (95% CI: 2.59 lower to 0.28 higher). Additionally, the MD in the level of depression was 0.39 lower (95% CI: 1.06 lower to 0.28 higher) (a lower value in each indicates a milder symptom). Although anxiety in family members yielded an RD of 58 more per 1000 (95% CI: 43 fewer to 191 more), depression yielded an RD of 19 fewer per 1000 (95% CI: 104 fewer to 80 more), and an SMD in the level of stress disorder was 0.09 lower (95% CI: 0.29 lower to 0.11 higher). There were no reports of adverse events resulting from applying an ICU diary. Based on these, we concluded that the balance of effects was probably better for the intervention (Data S3).

The RCTs included in the analysis had diverse target patients and families, as well as varying methods of ICU diary entries, such as the person making entries, entry method, timing, and duration. It is important to confirm the wishes of patients and their families prior to intervention and consider whether and how to provide the intervention.

CQ 8-5: Is follow-up after ICU discharge provided to families of critically ill patients to improve their mental health?

Answer: In facilities with well-established systems, we suggest providing follow-ups, such as face-to-face, phone, and online interviews after ICU discharge, to families of critically ill patients to improve their mental health (GRADE 2C).

Rationale

The PICS-F is a mental disorder that occurs in family members of critically ill patients when the patient is staying in the ICU, has been discharged from the ICU, or has passed away. Multiple studies have suggested that providing follow-up visits to family members of critically ill patient after the patient's discharge from the ICU is associated with a reduction in the psychological symptoms of family members and improvement in their QOL. However, its effectiveness and adverse events have not yet been validated.

We conducted a meta-analysis of eight RCTs.[587–594] As a result of providing follow-ups to the families of critically ill patients, such as face-to-face, phone, and online interviews after ICU discharge, the SMD in the level of family's depression was 0.03 higher (95% CI: 0.09 lower to 0.15 higher). However, the SMD in the level of anxiety was 0.03 lower (95% CI: 0.15 lower to 0.09 higher), and the SMD in the level of stress disorder was 0.01 lower (95% CI: 0.14 lower to 0.11 higher). The SMD in family's mental-related QOL was 0.06 lower (95% CI: 0.3 lower to 0.18 higher), and the SMD in overall health-related QOL was 0.11 lower (95% CI: 0.35 lower to 0.13 higher). There were no reports of adverse events resulting from the provision of follow-ups. As a result of examination with a focus on anxiety, depression, and stress disorders of families, we concluded that the balance of effects was probably better for the intervention (Data S3).

The RCTs included in the analysis had diverse targets and intervention methods, and interventions are expected to increase the workload of healthcare providers. Some interventions require families to pay their own medical expenses. Upon implementation, it is important to take into account the systems of one's own facility, confirm the wishes of a family in advance, and consider the content and implementation period of the follow-up.

CQ9 Pediatrics

Emergence of new diagnostic criteria for pediatric sepsis and septic shock: the Phoenix Sepsis Score

In 2016, the definition of sepsis in adult patients was revised to "sepsis-3," which focuses on infection-associated organ dysfunction. The problems encountered upon creating the

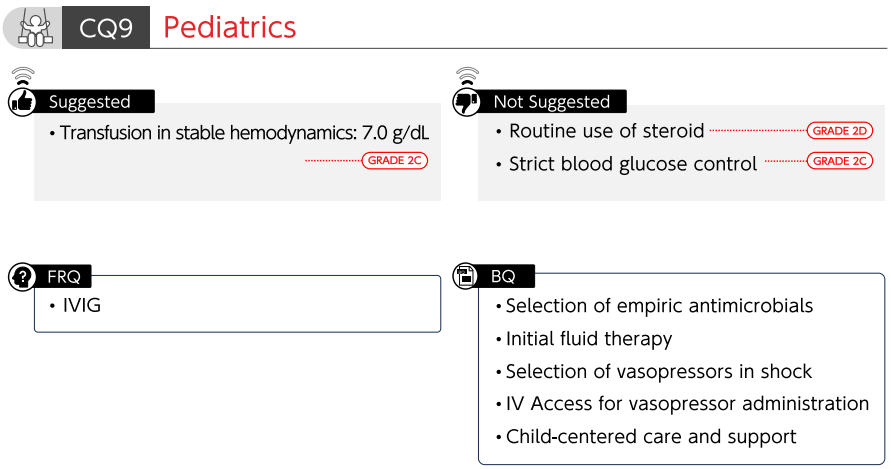

FIGURE 9 Summary of recommendations (CQ9 Pediatrics). BQ, background question; CQ, clinical question; FRQ, future research question; IV, intravenous; IVIG, intravenous immunoglobulin.

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TABLE 6 Phoenix Sepsis Score.

Variables	0 Points	1 Point	2 Points	3 Points
Respiratory (0–3 points)				
	PaO_2/F_IO_2 ratio ≥ 400 or SpO_2/F_IO_2 ≥292[a]	PaO_2/F_IO_2 ratio < 400 on any respiratory support or SpO_2/F_IO_2 ratio < 292 on any respiratory support[a,b]	PaO_2/F_IO_2 ratio 100–200 and IMV or SpO_2/F_IO_2 ratio 148–220 and IMV[a]	PaO_2/F_IO_2 ratio < 100 and IMV or SpO_2/F_IO_2 ratio < 148 and IMV[a]
Cardiovascular (0–6 points)				
		1 point each (up to 3) for:	2 points each (up to 6) for:	
	No vasoactive medications[c]	1 vasoactive medications[c]	≥2 vasoactive medications[c]	
	Lactate <5 mmol/L[d]	Lactate 5–10.9 mmol/L[d]	Lactate ≥11 mmol/L[d]	
Mean arterial pressure by age, mmHg[e,f]				
<1 month	>30	17–30	<17	
1–11 months	>38	25–38	<25	
1 to <2 years	>43	31–43	<31	
2 to <5 years	>44	32–44	<32	
5 to <12 years	>48	36–48	<36	
12 to <17 years	>51	38–51	<38	
Coagulation (0–2 points)[g]				
		1 point each (maximum of 2 points) for:		
	Platelets ≥100×10^3/μL	Platelets <100×10^3 /μL		
	International normalized ratio ≤ 1.3	International normalized ratio >1.3		
	D-dimer ≤2 mg/L FEU	D-dimer >2 mg/L FEU		
	Fibrinogen ≥100 mg/dL	Fibrinogen <100 mg/dL		
Neurological (0–2 points)[h]				
	Glasgow Coma Scale score > 10; pupils reactive[i]	Glasgow Coma Scale score ≤10[i]	Fixed pupils bilaterally	
Phoenix sepsis criteria				
Sepsis	Suspected infection and Phoenix Sepsis Score ≥2 points			
Septic shock	Sepsis with ≥1 cardiovascular point(s)			

Note: The Phoenix Sepsis Score may be calculated in the absence of some variables (e.g., even if lactate level is not measured and vasoactive medications are not used, a cardiovascular score can still be ascertained using blood pressure). It is expected that laboratory tests and other measurements will be obtained at the discretion of the medical team based on clinical assessment. Unmeasured variables contribute no points to the score. Ages are not adjusted for prematurity, and the criteria do not apply to birth hospitalizations, neonates whose postconceptional age is <37 weeks, or those aged ≥18 years.

Abbreviations: FEU, fibrinogen equivalent units; F_IO_2, fraction of inspired oxygen ratio; IMV, invasive mechanical ventilation; INR, international normalized ratio of prothrombin time; MAP, mean arterial pressure; PaO_2, arterial partial pressure of oxygen; SpO_2, oxygen saturation measured by pulse oximetry (only SpO_2 of ≤97%).

[a]SpO_2/F_IO_2 is only calculated if SpO_2 is ≤97% or.

[b]Respiratory dysfunction of 1 point can be assessed in any patient receiving oxygen, high-flow, non-invasive positive pressure, or IMV respiratory support, and includes a PaO_2/F_IO_2 ratio of <200 and SpO_2/F_IO_2 ratio of <220 in children who are not receiving IMV. For children receiving IMV with a PaO_2/F_IO_2 ratio of <200 and SpO_2/F_IO_2 ratio of <220, see the criteria for 2 and 3 points.

[c]Vasoactive medications include any dose of epinephrine, norepinephrine, dopamine, dobutamine, milrinone, and/or vasopressin (for shock).

[d]Lactate reference range between 0.5 and 2.2 mmol/L. Lactate can be arterial or venous.

[e]Age is not adjusted for prematurity, and the criteria do not apply to birth hospitalizations, children whose postconceptional age is <37 weeks, or those aged ≥18 years.

[f]Use measured MAP preferentially (invasive arterial if available or non-invasive oscillometry), and if measured MAP is not available, a calculated MAP (1/3 × systolic +2/3 × diastolic) may be used as an alternative.

[g]Coagulation variable reference ranges: platelets, $150–450 \times 10^3$/μL; D-dimer, <0.5 mg/L FEU; fibrinogen, 180–410 mg/dL. The INR reference range is based on the local reference prothrombin time.

[h]Neurological dysfunction sub score was pragmatically validated in both sedated and non-sedated patients, and those receiving or not receiving IMV support.

[i]The Glasgow Coma Scale score measures the level of consciousness based on verbal, eye, and motor response (range, 3–15, with a higher score indicating better neurological function).

"sepsis-3" criteria were; (1) internal validity was tested based only on reports from high- and middle-income countries; and (2) no decision was made on which indicators should be used to evaluate organ dysfunction in children. For these reasons, it has been considered inappropriate to directly apply "sepsis-3" to pediatric sepsis patients.[1]

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New sepsis diagnostic criteria for pediatric patients, called the Phoenix Sepsis Score (Table 6), was published in January 2024.[595,596] The Phoenix Sepsis Score assigns a score, ranging from 0 to 3, to each of four organ functions (respiratory, cardiovascular, coagulation, and neurological) in pediatric patients suspected of having an infection within 24 h of hospitalization. Among patients suspected of having an infection, those with the Phoenix Sepsis Score of ≥2 points are defined as having sepsis. Among pediatric patients with sepsis, those having cardiovascular dysfunction with the Phoenix Sepsis Score of ≥1 cardiovascular point are defined as having septic shock. The J-SSCG 2024 did not use the Phoenix Sepsis Score as a definition of sepsis, as it was published during the preparation of the J-SSCG2024. However, the Phoenix Sepsis Score is expected to be widely used as a new definition of pediatric sepsis in the future.

CQ 9-1: How are empiric antimicrobials selected for pediatric septic shock?

Answer: Antimicrobials for all possible microorganisms are selected, taking into account the organ of infection, setting (community, hospital, or ICU), and patient background (e.g., immune status and antimicrobial prescription history) (*Provision of information for background question*).

Rationale

Identification of infection focus is important in the treatment of pediatric sepsis, and it allows us to target causative microorganisms based on past epidemiological information. In pediatric patients with sepsis, a causative infection focus is often found in the respiratory or urinary tract system, and other possible locations include the abdominal cavity, skin/soft tissue, and central nervous system.[597–599]

If an infection focus can be identified based on medical history, physical findings, and various tests, we can estimate the causative microorganism based on patient's age, settings, and patient background, and select antimicrobials based on tissue penetration and antimicrobial spectrum.

If an infectious focus cannot be identified, empiric antimicrobials can be selected taking into consideration factors, such as age, settings, patient background, and tissue penetration. If the infectious focus is unknown in community-acquired pediatric sepsis patients, it is often found in the respiratory system, urinary tract system, or abdominal cavity,[597] and causative microorganism can be *Staphylococcus aureus*, or Enterobacteriaceae (such as *Escherichia coli*).[600] The causative microorganism in patients with nosocomial sepsis can also be glucose-non-fermentative bacteria, such as *Pseudomonas aeruginosa* and *Acinetobacter species*, in addition to Enterobacteriaceae, among other Gram-negative bacilli. It is noted that these must be affected by regional epidemiology or public health situation.[601] Additionally, patients with an underlying disease have an increasing risk of sepsis caused by methicillin-resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Clostridioides difficile*, or fungi.[602,603] Empiric antimicrobials effective to these microorganisms are selected considering the individual patient's background, risk of antibiotic-resistant pathogens, and severity of illness.

CQ 9-2: How is initial fluid therapy administered for pediatric sepsis?

Answer: Methods of administering initial fluid therapy to pediatric sepsis include repeated administration of balanced crystalloid solutions, as a 10–20 mL/kg bolus, while evaluating response to therapy. Clinical findings suggestive of fluid overload or poor response to fluid administration can serve as discontinuing fluid therapy. In particular, attention is paid to the amount and rate of bolus administration in patients complicated by heart failure. We cannot provide information regarding the speed of fluid administration or upper limit of total fluid volume (*Provision of information for background question*).

Rationale

In patients with sepsis complicated by tissue hypoperfusion or decreased blood pressure, initial fluid therapy is important for preventing the progression of organ dysfunction. In initial fluid therapy, a 20 mL/kg bolus of a modified crystalloid solution is first administered, which is then increased up to 40–60 mL/kg in the first hour until normal perfusion and blood pressure are achieved while monitoring for signs of fluid overload.[61] Previous high-quality studies that focused on the dosage and administration rate of initial fluids for pediatric patients with sepsis were small-scale. No significant difference in the mortality rate has been observed among different dosages and administration rates of fluid administration. Although there is no evidence that can be used for the recommendation on the superiority of saline or balanced crystalloids, the SSCG in Children 2020 suggested using balanced crystalloids.[604] When administering initial fluid therapy, responsiveness to fluid administration is frequently evaluated, and the speed of fluid administration and vasopressors are titrated. The effectiveness of initial fluid therapy is evaluated as needed using capillary refill time, lactate levels, and echocardiogram. If a patient exhibits insufficient response or signs of fluid overload, fluid loading is discontinued, and the use of vasopressors is considered.

CQ 9-3: How are vasopressors selected for pediatric patients with septic shock?

Answer: Adrenaline or noradrenaline is used as vasopressors in pediatric patients with septic shock, according to physical findings, hemodynamic parameters, and echocardiographic findings (*Provision of information for background question*).

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Rationale

It is reasonable to select noradrenaline in patients presenting with vasodilatory shock. Dopamine has a weaker α-receptor-stimulating effect than noradrenaline, and there is also a concern about an immunosuppressive effect due to the suppression of prolactin secretion via dopamine receptors. There is insufficient evidence for using dopamine as the first-line vasopressor, compared to adrenaline.[605,606] Vasopressin exerts a pressor effect through a mechanism different from that of catecholamines.[607,608] The responsiveness to first-line vasopressor, such as noradrenaline and adrenaline, is evaluated individually, and the additional use of vasopressin is considered. Physical findings, hemodynamic parameters, and echocardiogram should be comprehensively and repeatedly evaluated for each case when considering support with noradrenaline or adrenaline.

CQ 9-4: What is the route of administering vasopressors for pediatric sepsis?

Answer: Vasopressors are generally administered via the central venous line, as they may cause tissue injury when extravasation occurs. However, vasopressors are administered via a peripheral venous line or intraosseous access at appropriate concentrations for short periods to avoid delays in initiating the administration (*Provision of information for background question*).

Rationale

In the management of pediatric sepsis, prompt initiation of vasopressor administration is important for those who are unresponsive to initial fluid resuscitation. The administration of vasopressors through the peripheral venous line has the risk of developing extravasation, secondary tissue injury, and local perfusion deficits.[609] For this reason, they are generally administered through the central venous line.[610] However, placement of a central venous line requires time, leading to a delay in starting the administration of vasopressors. Some case series of children have suggested that the administration of vasopressors through a peripheral venous line is safe at appropriate concentrations for short periods.[609,611] A recent meta-analysis of adults and children found a very low incidence of extravasation or no serious events in children administered vasopressors through the peripheral venous line.[612] The relationship between the concentration of administered vasopressor and the incidence of extravasation is unclear.

CQ 9-5: Are steroids administered to pediatric patients with septic shock who are unresponsive to initial fluid therapy and vasopressors?

Answer: We suggest against routine administration of steroids for pediatric patients with septic shock who are unresponsive to initial fluid therapy and vasopressors (GRADE 2D).

Rationale

There has been a debate on the routine use of systemic steroids in pediatric patients with sepsis, and some high-quality studies have been published. We conducted meta-analyses of three RCTs.[613–615] With regard to the desirable effects of steroid administration, mortality yielded an RD of 57 fewer per 1000 (95% CI: 161 fewer to 100 more), and duration until recovery from shock yielded an MD of 3.3 days shorter (95% CI: 4.0 days shorter to 2.6 days shorter). In contrast, with regard to the undesirable effects of steroid administration, the length of hospital stay yielded an MD of 3.2 days longer (95% CI: 0.13 days shorter to 6.5 days longer), and infectious complications yielded an RD of 40 more per 1000 (95% CI: 68 fewer to 328 more). The desirable effects were small, and the undesirable effects were also small. Thus, we concluded that the balance of effects was neither intervention nor comparator was superior (Data S3).

CQ 9-6: What is the optimal hemoglobin level for blood transfusion in pediatric patients with sepsis who have stable hemodynamics?

Answer: We suggest transfusing at a hemoglobin level of 7.0 g/dL in hemodynamically stable pediatric patients with sepsis (GRADE 2C).

Rationale

Children may easily develop anemia due to lower normal hemoglobin levels or greater effects of blood sampling compared to adults. Hemoglobin has an important role in oxygen transport, and RBC transfusion therapy has been one of the most important therapeutic options. In contrast, the choice of whether or not to administer blood transfusion therapy is crucial, considering the detrimental effects of excessive blood transfusion and complications, such as infections and allergic reactions, as well as long-term post-treatment effects. We conducted a meta-analysis of three RCTs.[616–618] With regard to the desirable effects of setting a relatively low hemoglobin level, which determines the implementation of transfusion, hospital mortality yielded an RD of 117 fewer per 1000 (95% CI: 170 fewer to 22 fewer), new or progressive multiple organ dysfunction yielded an RD of 5 fewer per 1000 (95% CI: 46 fewer to 55 more), length of ICU stay yielded an MD of 1.78 days shorter (95% CI: 2.7 days shorter to 0.86 days shorter); and duration of mechanical ventilation yielded an MD of 1.02 days shorter (95% CI: 1.77 days shorter to 0.27 days shorter). Concerning the undesirable effects, ICU mortality yielded an RD of 9 more per 1000 (95% CI: 11 fewer to 57 more), and transfusion-related complications yielded an RD of 20 more per 1000 (95% CI: 48 fewer to 97 more). The desirable effects were small, and the undesirable effects were

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trivial. Considering the relative value of each outcome, we concluded that the balance of effects was probably better for the intervention (Data S3).

CQ 9-7: Is strict blood glucose control performed for pediatric sepsis?

Answer: We suggest against strict blood glucose control for pediatric sepsis (GRADE 2C).

Rationale

There are diverse opinions on the appropriateness of strict blood glucose control for pediatric patients with sepsis. The occurrence of hyperglycemia in severe pediatric patients may affect the immune function and exacerbate infections, leading to increased mortality and length of hospital stay. Hypoglycemia is a noteworthy harm of insulin therapy, and the occurrence of hypoglycemia is associated with worsened prognosis in critically ill patients. We conducted a meta-analysis of five RCTs.[619–623] With regard to the desirable effects of strict blood glucose control, the short-term mortality, which was the most important, yielded an RD of 2 more per 1000 (95% CI: 10 fewer to 19 more), length of ICU stay yielded an MD of 0.51 days shorter (95% CI: 0.53 days shorter to 0.49 days longer), and duration of mechanical ventilation yielded an MD of 0.30 days shorter (95% CI: 0.32 days shorter to 0.28 days longer). With regard to the undesirable effect of strict blood glucose control, hypoglycemia yielded an RD of 146 more per 1000 (95% CI: 108 more to 192 more). The desirable effects were trivial, and the undesirable effect were moderate. Thus, we concluded that the balance of effects was probably better for the comparator (Data S3).

CQ 9-8: What are treatment and support policies centered on critically ill pediatric patients?

Answer: It is necessary to support the decision-making that prioritizes the benefits of affected children and respects the values and wishes of the affected children and their families.

A multidisciplinary team has a role in providing appropriate medical information. Actively creating an environment that allows family members to participate in care and support the decision-making process is essential, especially in pediatric patients (*Provision of information for background question*).

Rationale

In order to support the decision-making of critically ill pediatric patients and their families, it is essential for a multidisciplinary team to provide accurate medical information about the potential risks and benefits of treatment. When considering treatment policy, healthcare providers should develop a sufficient care plan for family members of a patient who are entrusted with decisions on medical treatment, while prioritizing the benefits and values of the affected child.[567,624] There has been insufficient evidence on the optimal method for appropriately formulating care plans for critically ill pediatric patients and their families. It is necessary to formulate guidelines for each medical team and implement a comprehensive care plan centered on affected children. Its examples include having family members participate in medical team rounds, presenting information leaflets about the ICU to family members, introducing an ICU diary, engaging with family members in cooperation with multiple professions, working on noise reduction and environmental hygiene in the ICU, setting flexible or unrestricted family visits, and actively creating an environment that allows family members to spend time together. Healthcare providers aim to improve outcomes for pediatric patients and alleviate psychological burden on their families by prioritizing the improvement of the physiological conditions of affected children, formulating specific guidelines for family support, and supporting the decision-making process, while keeping in mind the particularity of pediatric medical care.

FRQ9-1: Is IVIG administered for pediatric sepsis?

Rationale

Intravenous immunoglobulin is occasionally administered to severe infections despite its effectiveness in improving clinical prognosis remains unclear. Although some studies have attempted to administer it in high doses for the purpose of immunomodulation, the studies have yielded inconsistent results, and there is a lack of high-quality RCTs of pediatric patients excluding neonates.[625–627] There have been weak recommendations against its use in adult patients with sepsis[72] and its routine administration to pediatric patients.[8,9,604] The evaluation of the effectiveness and harmfulness of IVIG has not been established. IVIG, which is a plasma fraction preparation, is not inexpensive, and clarifying its clinical efficacy is of great significance. It is worthwhile to summarize the information about IVIG, given the high mortality for pediatric sepsis patients.

Intravenous immunoglobulin is expected to have a pharmacological effect of reducing inflammation by exerting an immunoregulatory action through the enhancement of passive immunity due to neutralization of pathogenic microorganisms and toxins and suppression of inflammatory mediators.[8,9,604,628]

However, high-quality studies on IVIG in pediatric patients with sepsis are scarce. One RCT investigated the administration of polyclonal IVIG in 100 pediatric patients with sepsis, and its administration decreased the hospital mortality rate (28% vs. 56%), length of pediatric ICU stay (6.1 days vs. 9.1 days), and complications (8% vs. 32%).[629] However, it was a single-center, open-label RCT with a small sample size,

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no specification on the method of randomization, and the target population was limited to relatively young children (1 month to 2 years old). Thus, there were concerns, such as difficulty in extrapolating the study to all pediatric sepsis patients. The J-SSCG 2020 avoided creating a recommendation based only on this evidence.[8,9,604] The SSCG in Children 2020 states, "*We suggest against the routine administration of intravenous immunoglobulin to pediatric patients with septic shock or sepsis-related organ dysfunction (weak recommendation, low quality of evidence)*".[604]

The effectiveness of IVIG in adults is unfavorable, and the present guidelines, as well as the SSCG 2021, suggested against the administration of IVIG adult patients with sepsis.[72] Regarding neonates, a high-quality large-scale multicenter RCT conducted mainly on premature infants (the INIS trial),[630] as well as meta-analyses including the one for the RCT,[625,631] have clearly denied the treatment effect of IVIG on severe infections.

High-quality, large-scale multicenter RCTs of IVIG in pediatric patients are desired. When conducting the study, it is ideal that stratification is performed according to the type of infection (such as toxic shock syndrome or necrotizing fasciitis) and the presence or absence of comorbidities (such as hypogammaglobulinemia or immunodeficiency), resolving the uncertainty about the effectiveness of IVIG in each population.[401,408,632]

AUTHOR CONTRIBUTIONS

This guideline document was prepared by the 21 Guideline steering committee members (Panelists) and directors, 131 members of the guideline working group, and the systematic review group. NS (JSICM) and TN (JAAM) are the chairmen of this work, and both contributed equally to the creation of these guidelines. ME (JSICM) and SK (JAAM) are the organizers of the whole project and manuscript preparation. The names of the members are listed in the title page. Each member's contributions are shown in Data S3. All authors have read and approved the final manuscript.

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All committee members and working group members submitted disclosure forms of financial and academic conflict of interest (COI) prior to being requested to participate in individual activities. All COI were collected according to the guideline by the JSICM and the JAAM. Detailed information of COI and the roles in creating this clinical guideline are summarized in Data S4.

DATA AVAILABILITY STATEMENT

The datasets used and analyzed for systematic reviews are available from the corresponding author on reasonable request.

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ETHICS STATEMENT

Not applicable.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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